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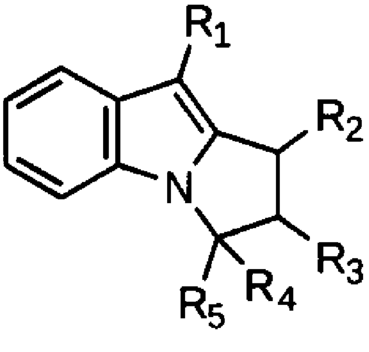
(54) **Title**: FLINDEROLE ANALOGUES AND PROCESS FOR SYNTHESIS THEREOF



(I)

(57) **Abstract**: The present invention discloses flinderole compounds/analogues of formula I and to a process for the preparation of same, comprising stereo- and regioselective [3+2] cycloaddition reaction of a tertiary alcohol (1a') and a sulphonated diene (1b') in presence of Lewis acid selected from Cu(OTf)2 or BF_3OEt_2 and a non-polar solvent at room temperature. The flinderole compounds /analogues of the instant invention and prepared by the process described therein is represented by the general formula I, (The formula I should be inserted here) wherein R1-R4 are described herein in the specification.

FLINDEROLE ANALOGUES AND PROCESS FOR SYNTHESIS THEREOF

FIELD OF THE INVENTION

The present invention provides a compound of general formula I and analogues thereof. Particularly, the present invention further discloses a highly stereo- and regioselective [3 +2] cycloaddition process for the preparation of Flinderole compound/analogues of general formula 1.

The present invention further provides compounds of general formula 1 which are useful as antimalarial compounds.

BACKGROUND AND PRIOR ART OF THE INVENTION

Malaria is a mosquito-borne infectious disease of humans and other animals caused by eukaryotic protists of the genus Plasmodium. Four strains of the parasite are responsible for malaria in humans, Plasmodium falciparum, P. vivax, P. ovale, and P. malariae. There were an estimated 225 million cases of malaria worldwide in 2009. Ninety percent of malaria-related deaths occur in sub-Saharan Africa, with the majority of deaths being young children. Plasmodium falciparum, the most severe form of malaria, is responsible for the vast majority of deaths associated with the disease. Malaria is commonly associated with poverty, and can indeed be a cause of poverty and a major hindrance to economic development.

With the continuous threat of evolution and rise of multi drug resistant strains of Plasmodium, particularly P. falciparum, there is a growing need to evolve alternatives to drugs such as Chloroquine, Artemisinin and such like. Research along these lines is being carried out to identify new compounds from various resources including plant, microbiological and synthetic.

To respond to the threat of resistance, structurally and functionally novel antimalarial compounds with new mechanisms of action are needed. There are articles and research papers which address flinderole compounds as antimalarial agents and the process for their synthesis. Nitrogen-containing heterocycles have been used as medicinal compounds for centuries, and form the basis for many common drugs such as Morphine (analgesic), Captopril (treatment of hypertension) and Vincristine (cancer chemotherapy).

The chemical structure of the flinderoles is based on the nitrogen-containing indole ring system; however, these compounds have a novel structure not reported in the literature, due to the attachment of the two indole rings. The flinderoles are related to the borreverine compounds, such as isoborreverine,

References may be made to an article titled "Flinderoles A–C: Antimalarial Bis-indole Alkaloids from *Flindersia* Species" by Liza S. Fernandez et.al in *Org. Lett.*, 2009, *11* (2), pp 329-332, discloses natural product antimalarials, the novel indole alkaloids flinderole A–C which have selective antimalarial activities with IC_{50} values between 0.15–1.42 μM. Flinderole A was isolated from the Australian plant *Flindersia acuminata* and flinderoles B and C from the Papua New Guinean plant *F. amboinensis*. The article further states that Flinderoles A-C contain an unprecedented rearranged skeleton compared to their related isomers of the borreverine class of compounds.

References may be made to PhD research paper titled "The Total Synthesis of the Antimalarial Natural Products, Flinderoles" discusses a methodology for the total synthesis of the novel bis-indole alkaloid ring-system found in the recently isolated natural products, the flinderoles. The thesis proposes two options for coupling the fragments together (Figure 1); a metathesis reaction between two terminal olefins, or a Wittig reaction between a phosphine and a carbonyl group on the respective fragments.

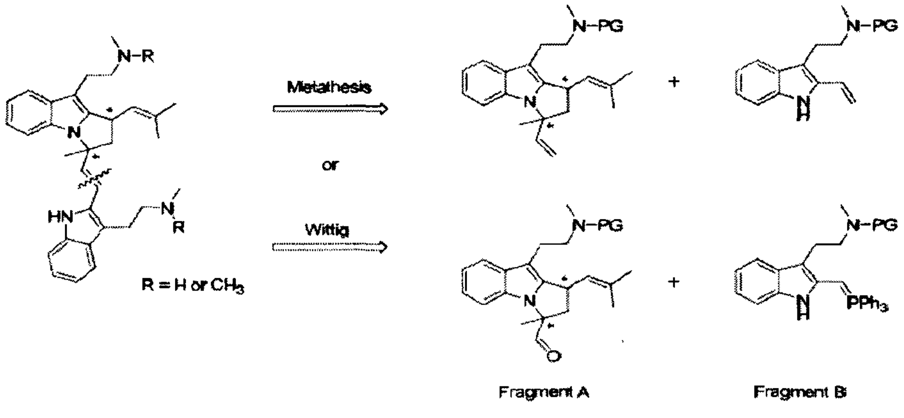


Figure 1. Proposed routes for coupling Fragments A and B.

The flinderoles disclosed in the prior art are either isolated from the natural sources which have the limitations in view of environmental, biodiversity issues etc. or are synthesized by lengthy, non-economical processes.

To bridge the gap in the therapy for malaria, and with the information that flinderole, isolated from natural product extract, present new molecular scaffold for antimalarial drug discovery, the inventors proposed to further research into these novel compounds for use as an agent against potent and resistant P.falciparum. Also, with the increasing prevalence of the infection, the inventors have also perceived the need to evolve a synthetic process for such effective compounds, such that the process fulfills the market needs for such effective compounds and also leads to compounds with enhanced bioactivity.

OBJECTS OF THE INVENTION

The main object of the present invention is to provide flinderole compounds /analogues of general formula I, excluding the proviso which comprises known Flinderoles A, B and C, as effective antimalarials.

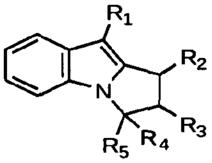
The another object of the invention is to provide a feasible, cost effective process for the preparation of Flinderoles and its analogues of general formula I as antimalarials especially for effective treatment against plasmodium falciparum.

Another object of the invention is to provide a highly stereo- and regioselective [3 +2] cycloaddition process for the preparation of Flinderole compound/analogues of general formula 1.

Yet another object of the present invention is to provide a process for the synthesis of compounds of formula I such that the process is useful for production of commercial quantities of such compounds with improved level of bioactivity.

SUMMARY OF THE INVENTION

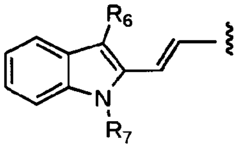
In an aspect, the present invention provides flinderole compounds /analogues of formula I, , excluding the provisos which comprises known Flinderoles A, B and C, as effective antimalarials.



Formula I

Wherein, R1 to R5 are described herein below.

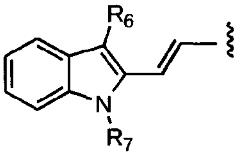
Flinderole compounds of formula I wherein (i) R_1 is $-CH_2CH_2NHMe$, R_2 is $-CH=CMe_2$,, R_3 is -H, R_5 is .....CH_3,

R_4=


;

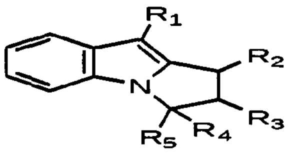
R_6 is $-CH_2CH_2NHMe$ and R_7 is -H;

and (ii) when R_1 is $--CH_2CH_2NMe_2$, R_2 is $-CH=CMe_2$, R_3 is -H, R_5 $-CH_3$,

R_4=


R_6 is $-CH_2CH_2NMe_2$ and R_7 is -H are known compounds in the art and represent Flinderoles A, B and C.

Accordingly, present invention provides compounds of general formula



General Formula I

wherein,

R_1 is selected independently from $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$,

-$CH_2CH_2CH_2CO_2H$, -$OCOCH_3$, -$OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, -$CH_2CO_2CH_3$, -$CH_2CO_2CH_2CH_3$, -COCH2Ph, -$COCH_2Ph$, -COCOCl, -$OCO(CH_2)_6Me$.

R_2 is selected independently from-$CH=CH_2$, -$CH=CHMe$, -$CH=CMe_2$, -$CH=CHEt$, -$CH=CEt_2$, -$CH=CH(Pr)$, -$CH=C(Pr)_2$, -$CH=CH(i\text{-}Pr)$, -$CH=C(i\text{-}Pr)_2$, -$CH=CHPh$, -$CH=C(Ph)_2$, -Ph, -PhCl, -$PhCH_3$, -PhOMe, -CH_2Ph, -CH_2PhCH_3, -CH_2PhOMe, -$CH(Me)_2$, -CH_2CH_3, -$C(Me)_3$, -C_6H_6, -$CH_2CH=CH_2$, -CHMeEt, -$CH_2C(Me)_3$, -$CH_2CH=CH_2$, -CCPh.

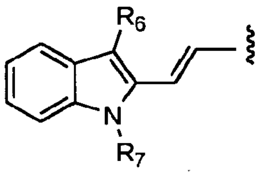
R_3 is selected independently from -H, CH3, -Ph, -CH_2CH_3, -$CH_2CH_2CH_3$, -Br, -Cl, -F, -I, -CH_2OH, -CH_2OCH_3, -CH_2OBn, -$CH_2OCH_2CH_3$, -CH_2CH_2OH, -CH_2CH_2Br, -$CH_2CH_2NH_2$, -CH_2CH_2NHMe, -$CH_2CH_2NMe_2$, -CH_2NH_2, -CH_2NHMe, CH_2NMe_2, - (4-Fluorophenyl), -CO_2H, -$CH_2CH=CH_2$, -$CH=CMe_2$, -$CH=CEt_2$, -OCH_3, OCH_2CH_3, -$COCH_3$, -OH, -CHO, -$CONH_2$, -CH_2CONH_2, -$CH_2CONHMe$, -CH_2CONMe_2, -$CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, -$CH_2CH_2CONMe_2$, -CN, -CH_2CN, -CH_2CO_2H, -CH_2CO_2Me, -CH_2CO_2Et, - (2-Nitrovinyl), -$CH_2=CHCO_2H$, -$CH=CHCO_2Me$, -$CH=CHCO_2Et$, -$CH_2=CHCN$, -$COCO_2H$, -$COCONH_2$, -COCONHMe, -$COCONMe_2$, -$CH_2CH_2CO_2H$, -$CONHNH_2$, -$CH_2CONHNH_2$, -$COCONMe_2$, -SH, -SC_2H_5, -$SCH=CH_2$, -$CH_2CH_2CH_2CO_2H$, -$OCOCH_3$, -$OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, -$CH_2CO_2CH_3$, -$CH_2CO_2CH_2CH_3$, -COCH2Ph, -$COCH_2Ph$, -COCOCl, -$OCO(CH_2)_6Me$.

R_4 is selected independently from -H, CH3, -Ph, -CH_2CH_3, -$CH_2CH_2CH_3$, -Br, -Cl, -F, -I, -CH_2OH, -CH_2OCH_3, -CH_2OBn, -$CH_2OCH_2CH_3$, -CH_2CH_2OH, -CH_2CH_2Br, -$CH_2CH_2NH_2$, -CH_2CH_2NHMe, -$CH_2CH_2NMe_2$, -CH_2NH_2, -CH_2NHMe, CH_2NMe_2, - (4-Fluorophenyl), -CO_2H, -$CH_2CH=CH_2$, -$CH=CMe_2$, -$CH=CEt_2$, -OCH_3, OCH_2CH_3, -$COCH_3$, -OH, -CHO, -$CONH_2$, -CH_2CONH_2, -$CH_2CONHMe$, -CH_2CONMe_2, -$CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, -$CH_2CH_2CONMe_2$, -CN, -CH_2CN, -CH_2CO_2H, -CH_2CO_2Me, -CH_2CO_2Et, - (2-Nitrovinyl), -$CH_2=CHCO_2H$, -$CH=CHCO_2Me$, -$CH=CHCO_2Et$, -$CH_2=CHCN$, -$COCO_2H$, -$COCONH_2$, -COCONHMe, -$COCONMe_2$, -$CH_2CH_2CO_2H$, -$CONHNH_2$, -$CH_2CONHNH_2$, -$COCONMe_2$, -SH, -SC_2H_5, -$SCH=CH_2$, -$CH_2CH_2CH_2CO_2H$, -$OCOCH_3$, -$OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, -$CH_2CO_2CH_3$, -$CH_2CO_2CH_2CH_3$, -COCH2Ph, -$COCH_2Ph$, -COCOCl, -$OCO(CH_2)_6Me$.

R_5 is selected independently from -CH3, -$CH=CH_2$, -$CH=CHMe$, -$CH=CMe_2$, -$CH=CHEt$, -$CH=CEt_2$, -$CH=CH(Pr)$, -$CH=C(Pr)_2$, -$CH=CH(i\text{-}Pr)$, -$CH=C(i\text{-}Pr)_2$, -$CH=CHPh$, -$CH=C(Ph)_2$, -$CH=CH$(Indole).

With the provisio, when R4 is as indicated herein below,

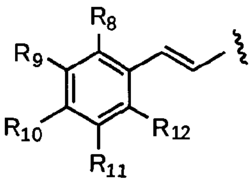
R_4=



R_6 selected from -H, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -Br, -Cl, -F, -I, -CH_2OH, -CH_2OCH_3, -CH_2OBn, -$CH_2OCH_2CH_3$, -CH_2CH_2OH, -CH_2CH_2Br, -$CH_2CH_2NH_2$, -CH_2CH_2NHMe, -$CH_2CH_2NMe_2$, -CH_2NH_2, -CH_2NHMe, CH_2NMe_2, - (4-Fluorophenyl), -CO_2H, -Ph, -$CH_2CH{=}CH_2$, -$CH{=}CMe_2$, -$CH{=}CEt_2$, -OCH_3, OCH_2CH_3, -$COCH_3$, -OH, -CHO, -$CONH_2$, -CH_2CONH_2, -$CH_2CONHMe$, -CH_2CONMe_2, -$CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, -$CH_2CH_2CONMe_2$, -CN, -CH_2CN, -CH_2CO_2H, -CH_2CO_2Me, -CH_2CO_2Et, - (2-Nitrovinyl), -$CH_2{=}CHCO_2H$, -$CH{=}CHCO_2Me$, -$CH{=}CHCO_2Et$, -$CH_2{=}CHCN$, -$COCO_2H$, -$COCONH_2$, -COCONHMe, -$COCONMe_2$, -$CH_2CH_2CO_2H$, -$CONHNH_2$, -$CH_2CONHNH_2$, -$COCONMe_2$, -SH, -SC_2H_5, -$SCH{=}CH_2$, -$CH_2CH_2CH_2CO_2H$, -$OCOCH_3$, -$OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, -$CH_2CO_2CH_3$, -$CH_2CO_2CH_2CH_3$, -COCH2Ph, -$COCH_2Ph$, -COCOCl, -$OCO(CH_2)_6Me$;

R_7 repesents -H, -CH_3, -$COCH_3$, -SO2Ph, -(BOC), -(Ph-F), -(Bn), -($C_5H_{10}F$), -(CO_2Et), -(MOM); with the provisio, when

R_4=



R_8 represents -H, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -Br, -Cl, -F, -I, -CH_2OH, -CH_2OCH_3, -CH_2OBn, -$CH_2OCH_2CH_3$, -CH_2CH_2OH, -CH_2CH_2Br, -$CH_2CH_2NH_2$, -CH_2CH_2NHMe, -$CH_2CH_2NMe_2$, -CH_2NH_2, -CH_2NHMe, CH_2NMe_2, - (4-Fluorophenyl), -CO_2H, -Ph, -$CH_2CH{=}CH_2$, -$CH{=}CMe_2$, -$CH{=}CEt_2$, -OCH_3, OCH_2CH_3, -$COCH_3$, -OH, -CHO, -$CONH_2$, -CH_2CONH_2, -$CH_2CONHMe$, -CH_2CONMe_2, -$CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, -$CH_2CH_2CONMe_2$, -CN, -CH_2CN, -CH_2CO_2H, -CH_2CO_2Me, -CH_2CO_2Et, - (2-Nitrovinyl), -$CH_2{=}CHCO_2H$, -$CH{=}CHCO_2Me$, -$CH{=}CHCO_2Et$, -$CH_2{=}CHCN$, -$COCO_2H$, -$COCONH_2$, -COCONHMe, -$COCONMe_2$, -$CH_2CH_2CO_2H$, -$CONHNH_2$, -$CH_2CONHNH_2$, -$COCONMe_2$, -SH, -SC_2H_5, -$SCH{=}CH_2$, -$CH_2CH_2CH_2CO_2H$, -$OCOCH_3$, -$OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, -$CH_2CO_2CH_3$, -$CH_2CO_2CH_2CH_3$, -COCH2Ph, -$COCH_2Ph$, -COCOCl, -$OCO(CH_2)_6Me$.

R_9 represents -H, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -Br, -Cl, -F, -I, -CH_2OH, -CH_2OCH_3, -CH_2OBn,

-$CH_2OCH_2CH_3$, -CH_2CH_2OH, -CH_2CH_2Br, -$CH_2CH_2NH_2$, -CH_2CH_2NHMe, -$CH_2CH_2NMe_2$, -CH_2NH_2, -CH_2NHMe, CH_2NMe_2, - (4-Fluorophenyl), -CO_2H, -Ph, -$CH_2CH=CH_2$, -$CH=CMe_2$, -$CH=CEt_2$, -OCH_3, OCH_2CH_3, -$COCH_3$, -OH, -CHO, -$CONH_2$, -CH_2CONH_2, -$CH_2CONHMe$, -CH_2CONMe_2, -$CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, -$CH_2CH_2CONMe_2$, -CN, -CH_2CN, -CH_2CO_2H, -CH_2CO_2Me, -CH_2CO_2Et, - (2-Nitrovinyl), -$CH_2=CHCO_2H$, -$CH=CHCO_2Me$, -$CH=CHCO_2Et$, -$CH_2=CHCN$, -$COCO_2H$, -$COCONH_2$, -$COCONHMe$, -$COCONMe_2$, -$CH_2CH_2CO_2H$, -$CONHNH_2$, -$CH_2CONHNH_2$, -$COCONMe_2$, -SH, -SC_2H_5, -$SCH=CH_2$, -$CH_2CH_2CH_2CO_2H$, -$OCOCH_3$, -$OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, -$CH_2CO_2CH_3$, -$CH_2CO_2CH_2CH_3$, -COCH2Ph, -$COCH_2Ph$, -COCOCl, -$OCO(CH_2)_6Me$.

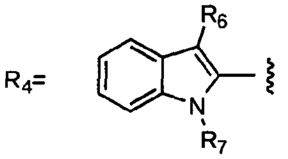
R_{10} represents -H, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -Br, -Cl, -F, -I, -CH_2OH, -CH_2OCH_3, -CH_2OBn, -$CH_2OCH_2CH_3$, -CH_2CH_2OH, -CH_2CH_2Br, -$CH_2CH_2NH_2$, -CH_2CH_2NHMe, -$CH_2CH_2NMe_2$, -CH_2NH_2, -CH_2NHMe, CH_2NMe_2, - (4-Fluorophenyl), -CO_2H, -Ph, -$CH_2CH=CH_2$, -$CH=CMe_2$, -$CH=CEt_2$, -OCH_3, OCH_2CH_3, -$COCH_3$, -OH, -CHO, -$CONH_2$, -CH_2CONH_2, -$CH_2CONHMe$, -CH_2CONMe_2, -$CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, -$CH_2CH_2CONMe_2$, -CN, -CH_2CN, -CH_2CO_2H, -CH_2CO_2Me, -CH_2CO_2Et, - (2-Nitrovinyl), -$CH_2=CHCO_2H$, -$CH=CHCO_2Me$, -$CH=CHCO_2Et$, -$CH_2=CHCN$, -$COCO_2H$, -$COCONH_2$, -$COCONHMe$, -$COCONMe_2$, -$CH_2CH_2CO_2H$, -$CONHNH_2$, -$CH_2CONHNH_2$, -$COCONMe_2$, -SH, -SC_2H_5, -$SCH=CH_2$, -$CH_2CH_2CH_2CO_2H$, -$OCOCH_3$, -$OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, -$CH_2CO_2CH_3$, -$CH_2CO_2CH_2CH_3$, -COCH2Ph, -$COCH_2Ph$, -COCOCl, -$OCO(CH_2)_6Me$.

R_{11} represents -H, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -Br, -Cl, -F, -I, -CH_2OH, -CH_2OCH_3, -CH_2OBn, -$CH_2OCH_2CH_3$, -CH_2CH_2OH, -CH_2CH_2Br, -$CH_2CH_2NH_2$, -CH_2CH_2NHMe, -$CH_2CH_2NMe_2$, -CH_2NH_2, -CH_2NHMe, CH_2NMe_2, - (4-Fluorophenyl), -CO_2H, -Ph, -$CH_2CH=CH_2$, -$CH=CMe_2$, -$CH=CEt_2$, -OCH_3, OCH_2CH_3, -$COCH_3$, -OH, -CHO, -$CONH_2$, -CH_2CONH_2, -$CH_2CONHMe$, -CH_2CONMe_2, -$CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, -$CH_2CH_2CONMe_2$, -CN, -CH_2CN, -CH_2CO_2H, -CH_2CO_2Me, -CH_2CO_2Et, - (2-Nitrovinyl), -$CH_2=CHCO_2H$, -$CH=CHCO_2Me$, -$CH=CHCO_2Et$, -$CH_2=CHCN$, -$COCO_2H$, -$COCONH_2$, -$COCONHMe$, -$COCONMe_2$, -$CH_2CH_2CO_2H$, -$CONHNH_2$, -$CH_2CONHNH_2$, -$COCONMe_2$, -SH, -SC_2H_5, -$SCH=CH_2$, -$CH_2CH_2CH_2CO_2H$, -$OCOCH_3$, -$OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, -$CH_2CO_2CH_3$, -$CH_2CO_2CH_2CH_3$, -COCH2Ph, -$COCH_2Ph$, -COCOCl, -$OCO(CH_2)_6Me$.

R_{12} represents -H, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -Br, -Cl, -F, -I, -CH_2OH, -CH_2OCH_3, -CH_2OBn, -$CH_2OCH_2CH_3$, -CH_2CH_2OH, -CH_2CH_2Br, -$CH_2CH_2NH_2$, -CH_2CH_2NHMe, -$CH_2CH_2NMe_2$, -CH_2NH_2, -CH_2NHMe, CH_2NMe_2, - (4-Fluorophenyl), -CO_2H, -Ph, -$CH_2CH=CH_2$, -$CH=CMe_2$, -$CH=CEt_2$,

$-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$.

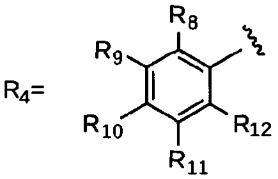
With the provisio, when R4 is as indicated herein below,



R_6 represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$.

R_7 = -H, $-CH_3$, $-COCH_3$, -SO2Ph, -(BOC), -(Ph-F), -(Bn), $-(C_5H_{10}F)$, $-(CO_2Et)$, -(MOM).

With the provisio, when



R_8 represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$,

$-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$.

R_9 represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$.

R_{10} represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$.

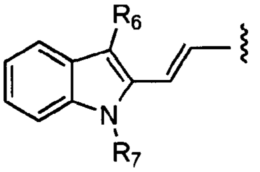
R_{11} represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$,

$-COCO_2H$, $-COCONH_2$, $-COCONHMe$, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, $-SH$, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$.

R_{12} represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, $-COCONHMe$, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, $-SH$, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$;

with the provisio, when R_1 is $-CH_2CH_2NHMe$, R_2 is $-CH=CMe_2$,, R_3 is –H, R_5 is .....CH_3,

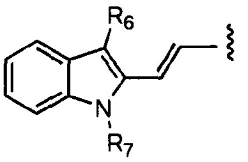
R_4=



R_6 is $-CH_2CH_2NHMe$ and R_7 is –H;

with the provisio, when R_1 is $--CH_2CH_2NMe_2$, R_2 is $-CH=CMe_2$, R_3 is –H, R_5 $-CH_3$,

R_4=



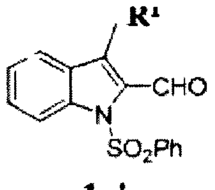
;

R_6 is $-CH_2CH_2NMe_2$ and R_7 is –H are excluded.

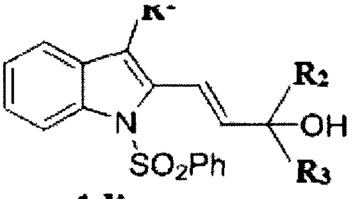
In an embodiment of the present invention, said compounds are useful as anti-malarial compound.

In yet another embodiment of the present invention, process for the preparation of Flinderole A-C and compounds of general formula I as claimed in claim 1 comprising the steps of:

a. reacting indole aldehyde (1c') with Ph3P=CHCO2Et followed by reaction of the resultant ester with MeMgBr to obtain tertiary alcohol (1d');

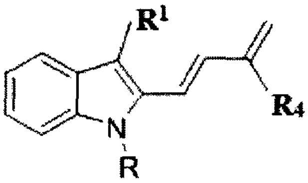


1c'



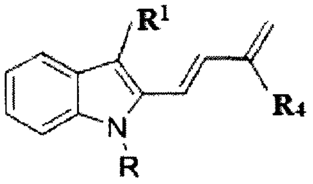
1d'

b. mesylating tertiary alcohol (1d') as obtained in step (a) followed by elimination to obtain sulphonated diene (1b');



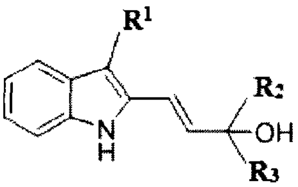
1b' R = SO₂Ph

c. desulfonylating (1b') as obtained in step (b) using methanolic NaOH to obtain desulphonated diene (1e');



1e' R = H

d. desulfonylating alcohol (1d') as obtained in step (a) with sodium amalgam to obtain alcohol (1a'); and

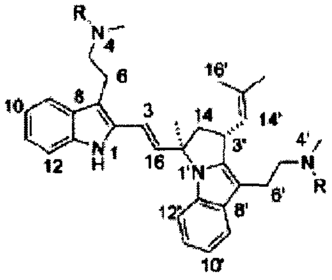


1a'

e. reacting alcohol (1a') as obtained in step (d) optionally with sulphonated diene

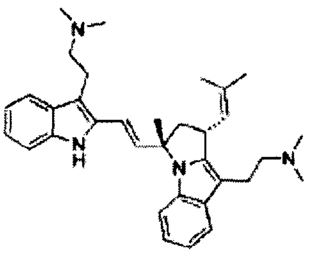
(1b') as obtained in step (b) or desulphonated diene (1e') as obtained in step (c) in presence of Lewis acid and a non- polar solvent at temperature in the range of 25 to 32°C to obtain sulphonated or desuphonated compound of general formula 1;

f. desulfonylating sulphonated compound of general formula 1 as obtained in step (e) using methanolic NaOH to obtain desulphonated Flinderole A-C and compounds of *general formula I* .

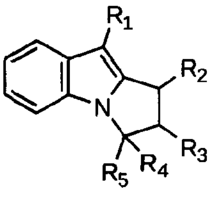


Flinderole A (R=H)

Flinderole B (R=H)



Flinderole C



General Formula I

In yet another embodiment of the present invention,Lewis acid used in step (e) is selected from Cu(OTf)2 or $BF_3{\cdot}OEt_2$.

In yet another embodiment of the present invention, the process for the preparation of compounds of general formula I, optionally comprising dimerization of alcohol (1a') and the said process comprising the steps of:

a. adding alcohol (1a') with lewis acid with stirring foer period in the range of 50 to 70 minutes at temperature in the range of 25 to 32°C followed by adding water to obtain reaction mixture;

b. extracting the reaction mixture as obtained in step (a) with non-polar solvent, washing with brine, drying followed by evaporating the solvent;

c. purifying the residue on silica gel column using EtOAc-hexane (1:39) to obtain compound of general formula 1.

In yet another embodiment of the present invention, Lewis acid used in step (a) is selected from Cu(OTf)2 or $BF_3{\cdot}OEt_2$.

In yet another embodiment of the present invention, a pharmaceutical composition for the treatment of malaria comprising compounds of general formula I optionally along with pharmaceutically acceptable excipients.

BRIEF DESCRIPTION OF THE FIGURES

Scheme 1 represents the cycloaddition reaction between a tertiary alcohol (1a′) and an olefin (1b′) to obtain compound of general formula 1.

Scheme 2 represents the structures of flinderoles A-C and the proposed biosynthetic pathway.

Scheme 3 represents flow chart for the preparation of compound of general formula 1.

Scheme 4 represents process steps for the preparation of intermediate compounds.

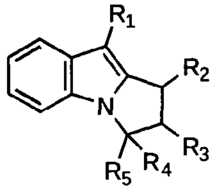
Scheme 5 represents compound 11 to 17 and process steps for the preparation of compound 9a, 9b, 10a and 10b.

Scheme 6 represents process steps for the preparation of compound 17-28 and flinderole B and C.

Figure 1' represents proposed stereo chemical model for the [3+2] cycloaddition.

DETAILED DESCRIPTION OF INVENTION

The present invention provides Flinderole compounds/ analogues of general formula I,



General formula 1

The present invention also relates to a highly stereo- and regioselective [3 +2] cycloaddition reaction between a tertiary alcohol (1a') and a diene (1b') (olefin) in presence of Lewis acid and a non-polar solvent at room temperature (25 to 32°C). (Scheme 1).

In an aspect, the process for the preparation of flinderoles of compounds/ analogues of formula I by the instsnt invention includes Flinderoles A, B and C.

Flinderoles A, B and C contain an unprecedented rearranged skeleton compared to their related isomers of the borreverine class of compounds. (Scheme 2)

Symmetrical retrosynthetic analysis of the dimeric structure of flinderoles revealed monomeric tryptamine diene as a possible precursor for the synthesis of flinderoles.

Exploration of the biosynthetic pathway as shown in Scheme 1 above lead to the conclusion that diene might undergo dimerization leading to the flinderole framework.

The diene (1e') is prepared from the known indole aldehyde (1c') (Scheme 3). Treatment of indole aldehyde (1c') with Ph3P=CHCO2Et followed by reaction of the resultant ester with MeMgBr generated the tertiary alcohol (1a'). Mesylation of alcohol (1a') and subsequent elimination yielded diene (1b'), which give the required diene (1e') upon desulfonylation using methanolic NaOH. The diene (1e') is found to polymerize with different Lewis acids under various reaction conditions employed, resulting in intractable mixtures. It is reasonably concluded that the actual site of protonation in 4 is at C3 of the indole nucleus to produce a conjugated enamine, which could undergo cationic polymerization.

At this juncture, it was reasoned that if diene (1e') is generated in situ in sufficiently low concentration, it might undergo dimerization by a formal intermolecular [3+2] cycloaddition, leading to the flinderole framework. Accordingly, the available alcohol (1d') is desulfonylated to obtain alcohol (1a') as shown in Scheme 3.

The pesent invention discloses the preparation of flinderoles 9a and 9b by dimerization of alcohol (8) in presence of various Lewis acids as shown in Scheme 4 nd Table 1 below.

Various Lewis acids were screened for the proposed dimerization of the alcohol 8 and results are summarized in **Table 1.**

Table 1: Invention and optimization of dimerization reaction of the alcohol (8)

entry	Lewis acid	Yield (%)	dr (9a:9b)
1	TMSOTf	10	1:1
2	Yb(OTf)$_3$	25	1:1
3	Sc(OTf)$_3$	25	1:1
4	BF_3·OEt$_2$	38	3:2
5	Cu(OTf)$_2$	46	2:1
6	CF_3CO_2H	35	3:2
7	Tf_2O	0	N.A.

Reaction of the alcohol (8) with TMSOTf furnished a complex mixture of products and the dimers (9a,b) were obtained in poor yield as 1:1 mixture of diastereomers (Table 1, entry 1). Similarly, $Yb(OTf)_3$ and $Sc(OTf)_3$ gave the desired adducts (9a,b) in low yield (Table 1, entries 2 and 3). $BF_3{\cdot}OEt_2$ was found to be useful catalyst for effecting this transformation in much cleaner manner generating the products (9a,b) albeit in moderate yield and diastereoselectivity (Table 1, entry 4). Even though Tf_2O did not give any desired product, trifluoroacetic acid did furnish the required product (9a,b) in comparable yield (Table 1, entries 6 and 7). More interestingly $Cu(OTf)_2$ generated the framework 9a and 9b in much improved yield and diastereoselectivity (Table 1, entry 5). The dimers 9a and 9b could be separated by careful column chromatography and their structures were established by spectroscopic analysis (^1H, ^{13}C, IR, HRMS) and with the comparison of spectral data. Their relative stereochemistry was determined by ROESY.

The scope of the dimerization reaction discussed above was further extended to reaction between the intermediate generated in situ of alcohol(1a') and the diene (1b') bearing a sulfonyl group in presence of Cu(OTf)2 to obtain flinderoles in good yield and diastereoselectivity. (Figure 1)

The present invention provides a highly stereo- and regioselective [3 +2] cycloaddition reaction between a tertiary alcohol (1a') and a sulphonated diene (1b') in presence of Lewis acid selected from Cu(OTf)2 or $BF_3{\cdot}OEt_2$ for the synthesis of flinderole compounds and its analogues of formula I comprising;

2. reacting indole aldehyde (1a') with Ph3P=CHCO2Et followed by reaction of the resultant ester with MeMgBr to obtain tertiary alcohol (1d');
3. mesylating alcohol (1d') followed by elimination to yield sulphonated diene (1b');
4. desulfonylating (1b') using methanolic NaOH to obtain diene (1e');
5. desulfonylating alcohol (1d') to obtain alcohol(1a'); and
6. reacting alcohol (1a') with sulphonated diene (1b') in presence of Lewis acid Cu(OTf)2 and a nono polar solvent at room temperature to obtain desired compounds of formula I.

The processes for the preparation of various Flinderoles are described in **Scheme 5** and **Scheme 6.**

Scheme 5 describes the dimerization reaction. Tert-alcohol 8 and the diene 7 are mixed together and treated with $Cu(OTf)_2$, the dimers 10a,b are obtained in requisite yield and diastereosectivity .($\geq$19:1). When $BF_3 \cdot OEt_2$ is used as catalyst, diastereomeric ratio drops to 2:1. Reaction is found to work with equal efficiency when tert-alcohol had ethyl rather than methyl substitution (cf. the adduct 11). Similarly, having an ethoxymethyl substituent on the C3 of indole did not affect the yield or selectivity (cf. the adducts 12 and 13)

According to Scheme 6, primary hydroxyl group of the compound 20 is acylated using acetic anhydride to furnish the acetate 21. Formylation of the acetate 21 using dichloromethyl methyl ether and stannic chloride gave the acetate 22. The acetyl protection in the indole derivative 22 is changed to TBS-protection following hydrolysis of acetate and reaction of the resultant alcohol with TBSCl to obtain TBS-ether 23. Wittig olefination of the aldehyde 23 with $Ph_3P{=}CHCO_2Et$ generated the unsaturated ester in 91% yield, which on treatment with methyl magnesium iodide give tertiary alcohol 24. Dehydration of the hydroxyl group of alcohol 24 is achieved via its mesylate followed by elimination to furnish the requisite olefin 19. Deprotection of the phenylsulfonyl group in alcohol 24 with sodium amalgam gives the other coupling partner, alcohol 18 (Scheme 6). An equimolar mixture of the tert alcohol 18 and the diene 19 are treated with catalytic amount of copper(II) triflate, which lead to the adduct 25a in 62% yield with diastereoselectivity. Surprisingly, when a mixture of the tert-alcohol 18 and the diene 19 is treated with excess of $BF_3 \cdot OEt_2$, not only it gives the expected dimerization product but also deprotected both TBDMS groups to directly generate the diols 26a,b. The major compound is found to be the isomer 26a in which the methyl and isobutylene groups are cis to each other. Oxidation of the mixture of the diols 26a,b using IBX followed by reductive amination of the resultant bisaldehydes 27a,b give a mixture of the amines 28a,b in 91% yield. Deprotection of indole nitrogen of 28a,b followed by purification by preparative TLC deliveres flinderole B (2) and flinderole C (3), which is treated individually with 0.005M TFA in acetonitrile to get the TFA salt of Flinderoles B and C. The TFA salt of synthetic flinderoles B and C thus obtained possess physical properties (IR, mass, ^1H, ^{13}C) identical to those reported in the literature.

Compounds of formula 9a and 9b are obtained by dimerization of alcohol (8). According to the process, to a solution of the alcohol **8** in anhydrous CH_2Cl_2 is added a catalytic amount of $Cu(OTf)_2$ and stirred magnetically for 1 h at RT. The progress of reaction is monitored by TLC till the starting alcohol had been completely consumed. Water is added to the reaction mixture, extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4. The solvent is evaporated followed by purification of the residue on silica gel column using EtOAc-hexane (1:39) as eluent to furnish isomer **9a.** Further, elution of the column with EtOAc-hexane (1:39) yield isomer **9b** as white crystalline solid.

In yet another embodiment, compound of formula 9a and 9b are obtained by **desulphonation of compounds of formula 10a and 10b using sodium amalgam as shown in Scheme 6.**

The flinderole compounds/analogues of formula I finds use in pharmaceutical industry, in agriculture; preferably in pharmaceutical industry for the treatment of malaria especially against Plasmodium falciparum.

The present invention provides a method of treatment or prevention of malaria to a subject by administering an effective amount of the compound of Formula I along with one or more suitable pharmaceutical carriers/excipients. The dosage forms include solid dosage forms such as tablets, powders, capsules, liquid dosage forms as well as parenteral dosage forms. The dosage forms can also be prepared as sustained, controlled, modified and immediate release dosage forms. Active ingredient(s) and excipients can be formulated into compositions and dosage forms according to methods known in the art.

In summary, a highly stereo- and regioselective formal [3+2] cycloaddition reaction between a tertiary alcohol (1a') and sulphonated olefin(1b') has been developed for use in the synthesis of pyrrolo[1,2-a] indoles, i.e Flinderole compounds/ analogues of formula I. The potential of this methodology has been amply demonstrated in the first total synthesis of the isomeric flinderoles B and C, which involves 11 steps in the longest linear sequence and gave an overall yield of 17.2%. The strategy is fairly general and is amenable to the synthesis of other natural products of this class as well as their analogues.

Examples

Following examples are given by way of illustration therefore should not be construed to limit the scope of the invention.

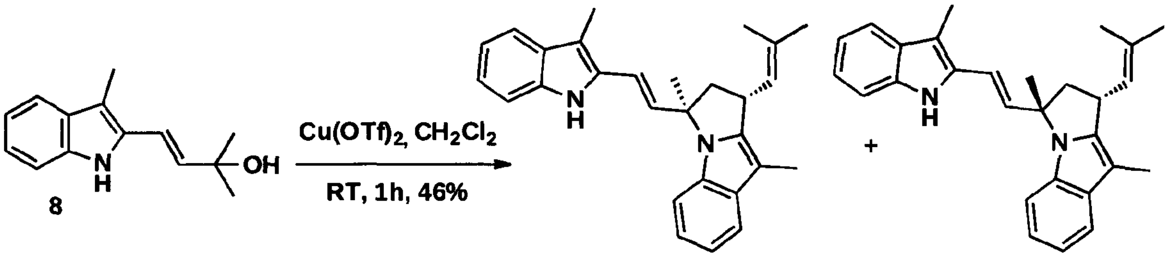
All reactions were carried out under nitrogen atmosphere with dry solvents under anhydrou conditions, unless otherwise mentioned. All the chemicals were purchased commercially, and used without further purification. Anhydrous THF and diethyl ether were distilled from sodium-benzophenone, and dichloromethane was distilled from calcium hydride. Yields refer to chromatographically pure material, unless otherwise stated.

Reaction were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as a visualizing agent and an p-anisaldehyde or ninhydrine stain, and heat as developing agents. Merck silica gel (particle size 100-200 and 230-400 mesh) was used for flash column chromatography. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. NMR spectra were recorded on either a Bruker Avance 200 (^{1}H: 200 MHz, ^{13}C: 50MHz), Bruker Avance 400 (^{1}H: 400 MHz, ^{13}C: 100MHz), Bruker Avance 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz). Mass spectrometric data were obtained using QTOF-Micromass-UK.

The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, ddd = doublet of a doublet of a doublet, dt = doublet of a triplet, m = multiplet, br = broad.

Example 1

Synthesis of compound 9a and 9b



9a, 31% 9b, 15%

To a solution of the alcohol 8 (50 mg, 0.23 mmol) in anhydrous CH_2Cl_2 (6 ml) was added a catalytic amount of $Cu(OTf)_2$ (15 mg, 0.04 mmol) and stirred magnetically for 1 h at RT. The progress of reaction was monitored by TLC till the starting alcohol has been completely consumed. Water (5 ml) was added to the reaction mixture, extracted with CH_2Cl_2 (3 x 5 ml), washed with brine (5 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:39) as eluent furnished the isomer 9a (28 mg, 31 %) as white crystalline solid; Rf = 0.5 (EtOAc-hexane 1:19);

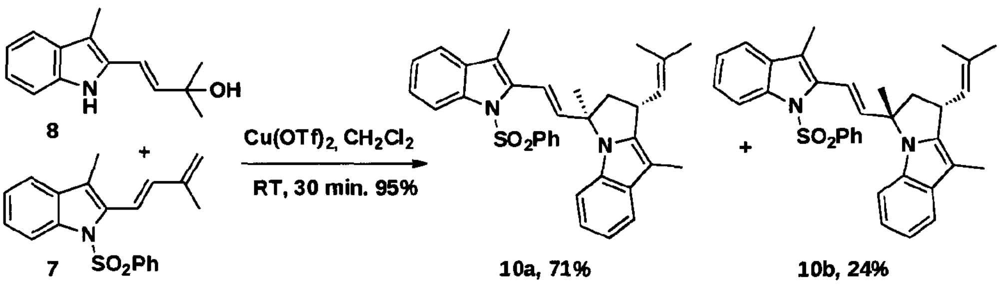
IR (neat): ν_{max}/cm^{-1} 3362, 3053, 2926, 1697, 1454, 1377, 789, 457; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.91 (br s, 1H), 7.60-6.95 (m, 8H), 6.80 (d, J = 16.6 Hz, 1H), 6.23 (d, J = 16.3 Hz, 1H), 5.27 (d, J = 9.3 Hz, 1H), 4.24 (q, J = 17.3 Hz, 1H), 2.69-2.60 (m, 1H), 2.41-2.30 (m, 4H), 2.20 (s, 3H), 1.82 (d, J = 16 Hz, 6H), 1.72 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 142.0, 136.2, 133.7, 133.1, 132.0, 131.2, 131.1, 129.9, 124.9, 123.1, 120.2, 119.5, 118.9, 118.5, 118.4, 118.3, 111.9, 110.4, 109.7, 101.8, 62.7, 52.0, 35.2, 25.7, 22.9, 18.2, 8.7, 7.9; HRMS: m/z calcd for $C_{28}H_{31}N_2$ [M+H$^+$]: 395.2487; found: 395.2496.

Further elution of the column with EtOAc-hexane (1:39) gave the isomer 9b (14 mg, 15%) as white crystalline solid; Rf = 0.45 (EtOAc-hexane 1:19).

IR (neat): ν_{max}/cm^{-1} 3479, 3410 (-NH), 3049, 2925, 1615, 1455, 1376, 1172, 973, 599; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.81 (br s, 1H), 7.60-7.00 (m, 8H), 6.22 (d, J = 16.3 Hz), 6.08 (d, J = 16.1 Hz, 1H), 5.28 (d, J = 9.3 Hz, 1H), 4.17 (q, J = 17.3 Hz, 1H), 2.80-2.75 (m, 1H), 2.35-2.25 (m, 1H), 2.20 (s, 3H), 2.17 (s, 3H), 1.94 (s, 3H), 1.8 (s, 6H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 142.6, 136.1, 133.7, 133.1, 131.4, 131.0, 129.4, 124.9, 122.9, 120.2, 119.4, 118.8, 118.5, 118.4, 117.1, 111.5, 110.3, 109.9, 101.7, 63.5, 51.9, 34.7, 25.9, 25.7, 18.2, 8.6, 7.8; HRMS: m/z calcd for $C_{28}H_{30}N_2Na$ [M+Na$^+$]: 395.2487; found: 395.2493.

Example 2

Synthesis of compound 10a and 10b:

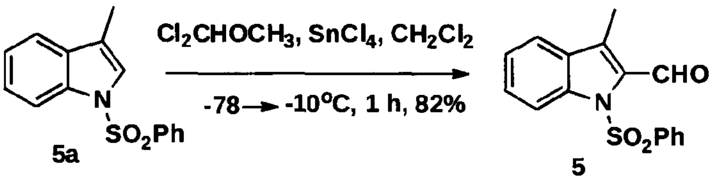


To a solution of the alcohol 8 (100 mg, 0.46 mmol) and diene 7 (156 mg, 0.46 mmol) in anhydrous CH_2Cl_2 (6 ml)was is added a catalytic amount of Cu(OTf)$_2$ (32.5 mg, 0.09 mmol) and stirred magnetically for 0.5 h at RT. The progress of reaction was monitored by TLC till the starting alcohol had been completely consumed. Water (5 ml) was added to the reaction mixture, extracted with CH_2Cl_2 (3 x 5 ml), washed with brine (5 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:99) as eluent furnished the isomer 10a (176 mg, 71 %) as white crystalline solid;

Rf = 0.5 (EtOAc-hexane 1:49); IR (neat): ν_{max}/cm^{-1} 2925, 1615, 1454, 1366, 1170, 967, 787, 603; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.18 (d, J = 8.1 Hz, 1H), 7.60-6.90 (m, 12H), 6.38 (d, J = 15.8 Hz, 1H), 5.98 (d, J = 16Hz, 1H), 5.32 (d, J = 9.3 Hz, 1H), 4.38 (q, J = 17.3 Hz, 1H), 2.90-2.80 (m, 1H), 2.28-2.39 (m, 1H), 2.23 (s, 3H), 2.15 (s, 3H), 2.02 (s, 3H), 1.83 (d, J = 4.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 142.7, 139.3, 138.3, 136.0, 133.8, 133.6, 133.3, 133.2, 131.5, 131.4, 128.8, 126.4, 124.9, 124.6, 123.5, 120.3, 119.0, 118.6, 118.5, 117.9, 114.8, 110.0, 101.8, 63.6, 51.2, 34.8, 25.7, 25.5, 18.2, 10.1, 7.8; HRMS: m/z calcd for $C_{34}H_{34}N_2O_2S$ Na [M+Na$^+$]: 557.2239; found: 557.2235.
Further elution of the column with EtOAc-hexane (1:99) gave the isomer 10b (60 mg, 24%) as white crystalline solid; Rf = 0.45 (EtOAc-hexane 1:49).

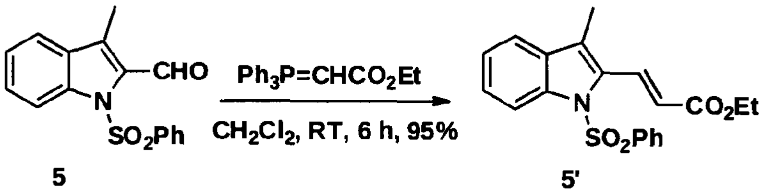
IR (neat): ν_{max}/cm^{-1} 2923, 1614, 1452, 1372, 1171, 972, 761, 471. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.18 (d, J = 7.3 Hz, 1H), 7.75-6.90 (m, 13H), 6.18 (d, J = 16.4 Hz, 1H), 5.32 (dt, J = 9.3, 1.4, 2.6 Hz, 1H), 4.27 (q, J = 16.9 Hz, 1H), 2.84-2.67 (m, 1H), 2.50-2.30 (m, 1H), 2.21 (s, 6H), 1.90-1.70 (m, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 142.1, 140.6, 138.2, 136.3, 133.6, 133.5, 133.4, 133.2, 131.8, 131.1, 128.9, 126.5, 125.1, 125.0, 123.7, 120.2, 120.0, 119.2, 119.0, 118.5, 115.0, 109.7, 101.8, 62.7, 52.0, 35.1, 25.7, 22.6, 18.2, 10.4, 7.81; HRMS: m/z calcd for $C_{34}H_{34}N_2O_2S$ Na [M+Na$^+$]: 557.2239; found: 557.2237.

Example 3: Synthesis of compound 5:



To a magnetically stirred solution of the indole **5a** (30 g, 110.7 mmol) in CH_2Cl_2 (130 ml) was added dichloromethyl methyl ether (34.4 ml, 387.5 mmol) followed by dropwise addition of $SnCl_4$ (45.4 ml, 387.5 mmol) at -78 °C, the mixture was allowed to come to -10 °C slowly over a period of 1h. 1.0 *N* HCl (20 ml) was added to the reaction mixture and extracted with CH_2Cl_2. The organic layer is washed with brine and dried over Na_2SO_4. Evaporation of the solvent and recrystallization of the crude product from 1,2-dichloroethane furnished the aldehyde **5** (27 g, 82%) as a white crystalline solid;

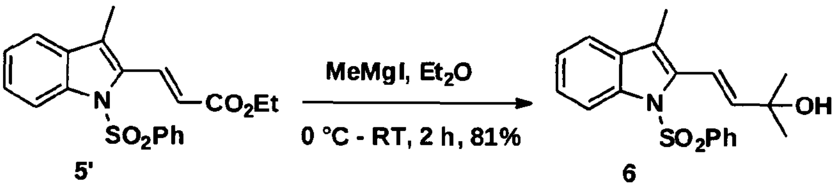
Rf = 0.4 (EtOAc -hexane 1:9); **IR** (neat): ν_{max}/cm^{-1} 2924, 2855, 2725, 1676 (C=O), 1462, 1365, 1173, 955, 722, 601; ^{1}**H NMR** ($CDCl_3$, 200 MHz): δ 10.60 (s, 1H), 8.22 (dt, *J* = 8.3 Hz, 1H), 7.75-7.60 (m, 2H), 7.60-7.20 (m, 6H), 2.51 (s, 3H); ^{13}**C NMR** ($CDCl_3$, 50 MHz): δ 185.2, 137.5, 137.0, 134.1, 133.0, 132.5, 130.6, 129.2, 129.2, 126.7, 124.8, 121.7, 115.8, 10.5; **HRMS**: m/z calcd for $C_{16}H_{13}NO_3S$ [M+H$^+$]: 300.0694; found: 300.0686.
Example 4: Synthesis of compound 5':



To a solution of the aldehyde **5** (12 g, 40.13 mmol) in anhydrous CH_2Cl_2 (200 ml) was added dry $Ph_3P=CHCO_2Et$ (20.9 g, 60.2 mmol) and stirred magnetically for 6 h at RT. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc -hexane (1.5:8.5) as eluent gave the ester **5'** (14 g, 95 %) as white crystalline solid;

Rf = 0.45 (EtOAc -hexane 3:7); **IR** (neat): ν_{max}/cm^{-1} 2984, 1712 (O-C=O), 1623, 1445, 1371, 1170, 982, 760, 598; ^{1}**H NMR** ($CDCl_3$, 200 MHz): δ 8.25 (m, 2 H), 8.21 (m, 1H), 7.75-7.60 (m, 2H), 7.55-7.20 (m, 6H), 6.12 (d, *J* = 16.2 Hz, 1 H), 4.33 (q, *J* = 7.14, 2H), 2.31 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}**C NMR** ($CDCl_3$, 50 MHz): δ 166.40, 137.8, 137.1, 134.5, 133.8, 131.8, 131.5, 129.0, 126.7, 126.5, 124.2, 123.5, 122.6, 119.9, 115.4, 60.8, 14.4, 10.9; **HRMS**: m/z calcd for $C_{20}H_{19}NO_4SNa$ [M+Na$^+$]: 392.0935; found: 392.0933.

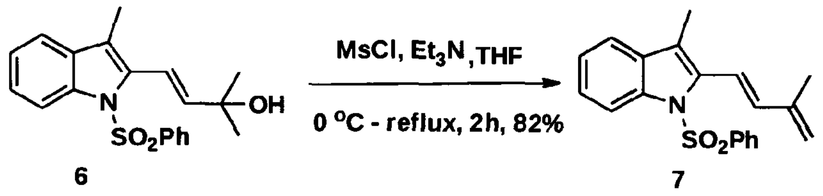
Example 5: Synthesis of compound 6:



To a cold (0 °C), magnetically stirred solution of the ester **5'** (10.0 g, 27.1 mmol) was added methyl magnesium iodide [prepared from magnesium turnings (2.6 g, 108.4 mmol), methyl iodide (10.1 ml, 162.6 mmol) and few crystals of iodine in anhydrous ether (50 ml)] and stirred for 2 h at RT. The reaction mixture was quenched with aq.NH_4Cl solution (50 ml) and worked up. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:4) as eluent furnished the tertiary alcohol **6** (7.8 g, 81%) as a white solid;

Rf = 0.4 (EtOAc -hexane 2:3); **IR** (neat): ν_{max}/cm^{-1} 2853, 1583, 1455, 1170, 963, 725, 595; ^{1}**H NMR** ($CDCl_3$, 200 MHz): δ 8.20 (dt, *J* = 7.20, 1H), 7.75-7.60 (m, 2H), 7.50-7.15 (m, 6H), 7.00-6.85 (m, 1H), 5.94 (d, *J* = 16.2 Hz, 1H), 2.18 (br s, 1H), 2.18 (s, 3 H), 1.50 (s, 6H); ^{13}**C NMR** ($CDCl_3$, 50 MHz): δ 144.4, 138.4, 136.3, 133.9, 133.5, 131.9, 128.9, 126.7, 125.0, 123.7, 119.1, 118.2, 117.1, 115.1, 71.2, 29.7, 10.2; **HRMS**: m/z calcd for $C_{20}H_{21}NO_3S$ Na [M+Na$^+$]: 378.1142; found: 378.1139.

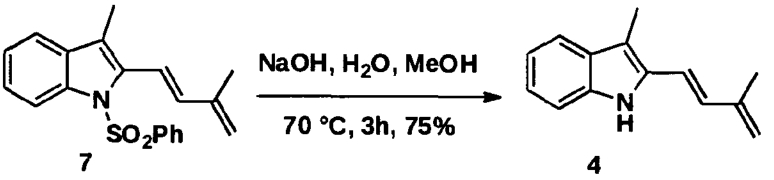
Example 6: Synthesis of compound 7:



To a solution of the alcohol **6** (3.6 g, 10.14 mmol) in anhydrous THF (50 ml) and Et_3N (8.45 ml, 60.84 mmol) under N_2 atmosphere was added MsCl (2.35 ml, 30.42 mmol) slowly over a period of 5 min at 0 °C. The solution was allowed to warm to RT for about 1.5 h and then refluxed for 30 min. The precipitate formed is filtered off using ethyl acetate affording a brown viscous liquid. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:9) as eluent furnished the diene **7** (2.8 g, 82%) as a white solid;

Rf = 0.5. (EtOAc-hexane 1:9); **IR** (neat): ν_{max}/cm^{-1} 2919, 1447, 1363, 1171, 968, 755, 603; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 8.30-7.20 (m, 9H), 7.04 (d, *J* = 16.3Hz, 1H), 6.43 (d, *J* = 16.3 Hz, 1H), 5.14 (d, *J* = 4.9 Hz, 2H), 2.25 (s, 3H), 2.08 (s, 3H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 142.3, 137.4, 133.5, 128.9, 126.7, 125.0, 123.8, 119.4, 119.1, 118.1, 115.2, 18.5, 10.6; **HRMS**: m/z calcd for $C_{20}H_{20}NO_2S$ $[M+H^+]$: 338.1214; found: 338.1208.

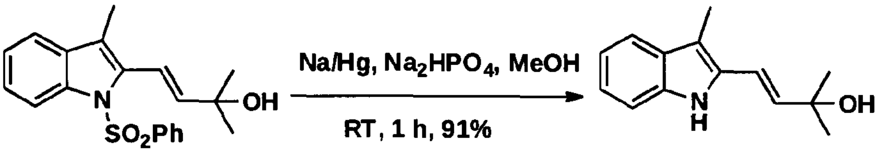
Example 7: Synthesis of compound 4:



To a solution of the protected diene **7** (2.5 g, 7.4 mmol) in MeOH (30 ml) is added NaOH (3 g, 74.2 mmol) in H_2O (10 ml) and the reaction mixture was heated to 70 °C for 3 h. Excess MeOH was removed under reduced pressure. The residue was washed with ether (3 x 20 ml). The organic extracts were combined, washed with brine (20 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:3) as eluent gave the diene **4** (1.1 g, 75%) as a yellow solid;

Rf = 0.35 (EtOAc-hexane 1:1); **IR** (neat): ν_{max}/cm^{-1} 3414, 1644, 1449, 1215, 1022, 756.5, 666.9; **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 9.24 (br s, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.13 (ddd, *J* = 1.2 Hz, 7.3 Hz, 8.2 Hz, 1H), 7.01 (ddd, *J* = 0.9 Hz, 7.0 Hz, 7.9 Hz, 1H), 6.78 (d, *J* = 16.2 Hz, 1H), 6.71 (d, *J* = 16.2 Hz, 1H), 5.11 (d, *J* = 19.8 Hz, 2H), 2.33 (s, 3H), 2.01 (s, 3H); **^{13}C NMR** ($CDCl_3$, 120 MHz): δ 143.5, 137.8, 133.6, 130.3, 130.2, 123.7, 120.0, 119.5, 117.2, 112.4, 111.4, 18.6, 8.7; **HRMS**: m/z calcd for $C_{14}H_{15}N$ [M+H$^+$]: 198.1204; found: 198.0914.

Example 8: Synthesis of compound 8:

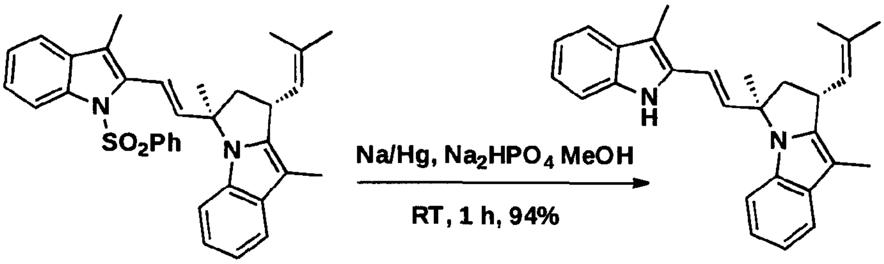


6 8

To a solution of the alcohol **6** (6 g, 16.9 mmol) in anhydrous methanol (50 ml) was added Na_2HPO_4 (9.6 g, 67.6 mmol) and Na-Hg (15.5 g, 67.6 mmol). The reaction mixture was stirred for 1 h at RT until all of the amalgam had become converted to liquid mercury. Water (20 ml) and ether (40 ml) were added and the supernatant was decanted. The residue was washed with ether (3 x 20 ml). The organic extracts were combined, washed with brine (20 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:3) as eluent gave the alcohol **8** (3.3 g, 91%) as a yellow solid;

Rf = 0.35 (EtOAc-hexane 1:1); **IR** (neat): v_{max}/cm^{-1} 3362 (OH), 3056 (NH), 2864, 1583, 1377, 1086, 786; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 7.98 (br s, 1H), 7.60-7.00 (m, 4H), 6.74 (d, *J* = 16.3 Hz, 1H), 6.08 (d, *J* = 16.2 Hz, 1H), 2.33 (s, 3 H), 1.64 (br s, 1H), 1.46 (s, 6H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 136.27, 134.78, 131.38, 129.61, 122.83, 119.37, 118.88, 115.73, 111.49, 110.38, 71.23, 30.04, 8.65; **HRMS**: m/z calcd for $C_{14}H_{16}N$ [M-OH$^-$]: 198.1283; found: 198.1281.

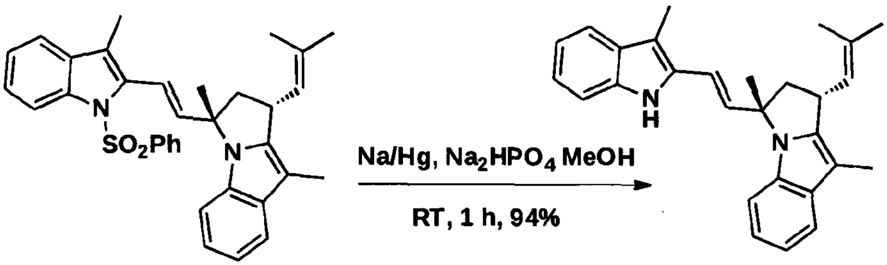
Example 9: Synthesis of compound 9a:



10a 9a

To a solution of the **10a** (50 mg, 0.09 mmol) in anhydrous methanol (6 ml) was added Na_2HPO_4 (56 mg, 0.36 mmol) and Na-Hg (82 mg, 0.36 mmol). The reaction mixture was stirred for 1 h at RT until all of the amalgam had become liquid mercury. Water (5 ml) and ether (10 ml) were added and the supernatant solution was decanted, extracted with ether (3 x 5 ml), washed with brine (5 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:39) furnished the compound **9a** (35 mg, 94%) as a white solid; *Rf* = 0.5 (EtOAc-hexane 1:19); whose data (IR, ^1H NMR, ^{13}C NMR and HRMS) was identical with earlier compound **9a** obtained from dimerization of *tert*-alcohol **8**.

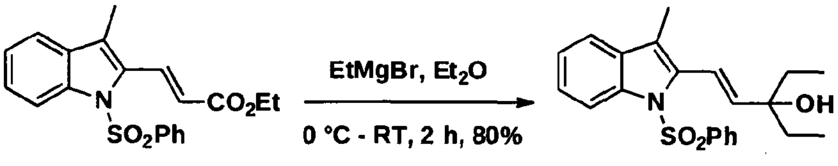
Example 10: Synthesis of compound 9b:



10b **9b**

To a solution of the **10b** (50 mg, 0.09 mmol) in anhydrous methanol (6 ml) was added Na_2HPO_4 (56 mg, 0.36 mmol) and Na-Hg (82 mg, 0.36 mmol). The reaction mixture was stirred for 1 h at RT until all of the amalgam had become converted into liquid mercury. Water (5 ml) was added to the reaction mixture, extracted with ether (3 x 5 ml), washed with brine (5 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:39) as eluent gave the compound **9b** (35 mg, 94%) as a white solid *Rf* = 0.45 (EtOAc-hexane 1:19); whose data (IR, ^1H NMR, ^{13}C NMR and HRMS) was identical with earlier compound **9b** obtained from dimerization of *tert*-alcohol **8**.

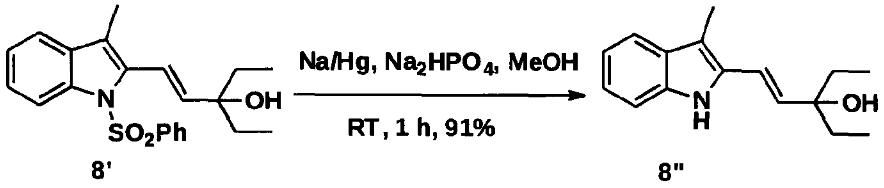
Example 11: Synthesis of compound 8':



5' **8'**

To a cold (0 °C), magnetically stirred solution of the ester **5'** (1 g, 2.71 mmol) was added methyl magnesium iodide [prepared from magnesium turnings (395 mg, 16.3 mmol), ethyl bromide (1.4 ml, 19.0 mmol) and few crystals of iodine in anhydrous ether (15 ml)] and stirred for 2 h at RT. The reaction mixture was then quenched with aq.NH_4Cl solution (10 ml) and worked up. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc:hexane (1:4) as eluent furnished the tertiary alcohol **8'** (800 mg, 80%) as a white solid; *Rf* = 0.4 (EtOAc -hexane 1:4). **IR** (neat): ν_{max}/cm^{-1} 1879, 1724, 1584, 1449, 1372, 1271, 1174, 1091, 1023, 980.4, 758.9, 592.0; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 8.19 (dd, *J* = 1.5, 7.1 Hz, 1H), 7.74-7.68 (m, 2H), 7.49-7.19 (m, 6H), 6.99 (d, *J* = 16.9 Hz, 1H), 5.85 (d, *J* = 16.3 Hz, 1H), 2.21 (s, 3H), 1.72 (q, *J* = 7.6, 15.3 Hz, 4H), 0.99 (t, *J* = 7.5Hz, 6H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 142.1, 138.4, 136.1, 134.3, 133.4, 131.8, 128.8, 126.5, 124.8, 123.6, 119.0, 118.8, 117.9, 115.0, 75.9, 33.0, 10.3, 7.9; **HRMS-ESI**: m/z calcd for $C_{22}H_{25}NO_3S$ Na [M+Na$^+$]: 422.1555; found: 422.1107.

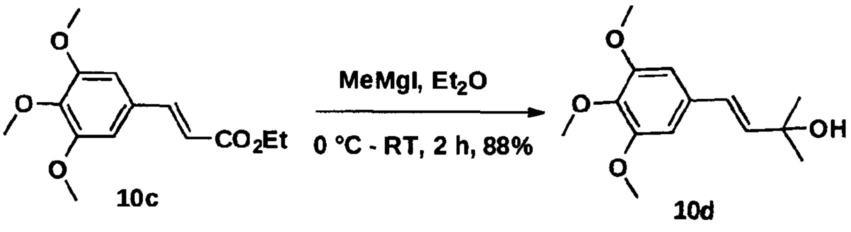
Example 12: Synthesis of compound 8":



To a solution of the alcohol **8'** (230 mg, 0.59 mmol) in anhydrous methanol (5ml) was added Na_2HPO_4 (339 mg, 2.38 mmol) and Na-Hg (548 mg, 2.36 mmol). The reaction mixture was stirred for 1 h at RT until all of the amalgam had become converted to liquid mercury. Water (5 ml) and ether (10 ml) were added and the supernatant was decanted. The residue was washed with ether (3 x 5ml). The organic extracts were combined, washed with brine (5 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:4) as eluent gave the alcohol **8"** (148 mg, 91%) as a yellow solid;

Rf = 0.5 (EtOAc-hexane 1:4); **IR** (neat): ν_{max}/cm^{-1} 2929, 1654, 1523, 1457, 1246, 872.6, 788.2; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 9.18 (br s, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.14-6.96 (m, 2H), 6.69 (d, *J* = 16.2 Hz, 1H), 6.07 (d, *J* = 16.3 Hz, 1H), 2.3 (s, 3H), 1.61 (q, *J* = 7.2, 15.2 Hz, 4H), 0.89 (t, *J* = 7.6 Hz, 6H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 137.8, 135.5, 133.8, 130.7, 123.5, 120.1, 119.7, 117.9, 111.7, 110.6, 76.54, 34.6, 9.0, 8.7; **HRMS-ESI**: m/z calcd for $C_{16}H_{21}NO$ [M+H$^+$]: 244.1701; found: 244.1709.

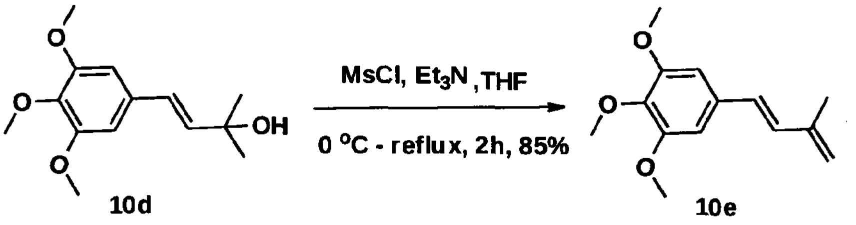
Example 13: Synthesis of compound 10d



To a magnetically stirred solution of methylmagnesium iodide, [prepared from magnesium turnings (2.8 g, 112.8 mmol), methyl iodide (9.37 ml, 150.4 mmol) and few crystals of iodine in anhydrous ether (50 ml)] was added slowly a mixture of the ester **10c** (11 g, 37.6 mmol) in anhydrous ether (40 ml). The reaction mixture was stirred for 2 h at RT. It was then quenched with aq. NH_4Cl solution (40 ml), extracted with ethyl acetate (3 x 15 ml), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc-hexane (2:8) as eluent furnished the alcohol **10d** (9.2 g, 88%) as a white solid.

Rf = 0.3 (EtOAc-hexane 1:3); **IR** (neat): ν_{max}/cm^{-1} 3436 (OH), 2975, 1584, 1215, 1129, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.60 (s, 2H), 6.51 (d, *J* = 16.1 Hz, 1H), 6.27 (d, *J* = 16.1 Hz, 1H), 3.85(d *J* = 5.3 Hz, 9H), 2.11 (br s, 1H), 1.43 (s, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 153.3, 137.5, 137.1, 132.7, 126.3, 103.3, 70.9, 60.9, 56.0, 29.9; **HRMS-ESI**: m/z calcd for $C_{19}H_{17}NO_5SNa$ [M+Na$^+$]: 275.1259; found: 275.1266.

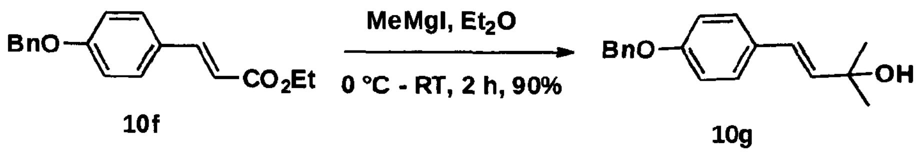
Example 14: Synthesis of compound 10e:



To a solution of the alcohol **10d** (8.0 g, 31.7 mmol) in anhydrous THF (60 ml) and Et_3N (26.3 ml, 190.6 mmol) under N_2 atmosphere was added MsCl (7.35 ml, 95.1 mmol) slowly over a period of 5 min at 0 °C. The solution was allowed to warm at RT for 1.5 h and then refluxed for 30 min. The precipitate formed was filtered off using ethyl acetate affording a colourless viscous liquid. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:9) as eluent furnished the diene **10e** (6.3 g, 85%) as a colourless viscous liquid

Rf = 0.5 (EtOAc-hexane 1:4); **IR** (neat): ν_{max}/cm^{-1} 2938, 2838, 1584, 1507, 1463, 1419, 1239, 1130, 1007, 667; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.80 (d, *J* = 16.1, 1H), 6.66 (s, 2H), 6.46 (d, *J* = 16.1 Hz, 1H), 5.1(d, *J* = 9.8 Hz, 2H), 3.87 (d, *J* = 6.9 Hz, 9H), 1.97 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 153.3, 141.9, 137.7, 133.1, 131.2, 128.6, 117.2, 103.5, 77.7, 77.1, 76.4, 60.9, 56.0, 18.6; **HRMS-ESI**: m/z calcd for $C_{14}H_{18}O_3K$ [M+K$^+$]: 273.0893; found: 273.0887.

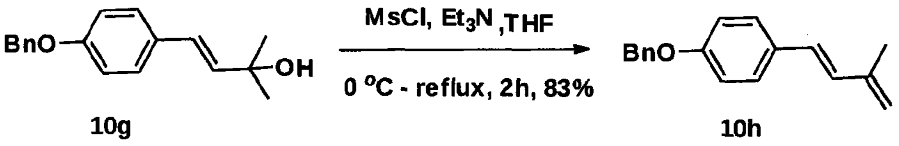
Example 15: Synthesis of compound 10g:



To a magnetically stirred solution of methylmagnesium iodide, [prepared from magnesium turnings (3.4 g, 138.1 mmol), methyl iodide (11.5 ml, 184.4 mmol) and few crystals of iodine in anhydrous ether (50 ml)] was added slowly a mixture of the ester **10f** (13 g, 46.1 mmol) in anhydrous ether (50 ml). The reaction mixture was stirred for 2 h at RT. It was then quenched with aq. NH_4Cl solution (50 ml), extracted with ethyl acetate (3 x 15 ml), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc-hexane (1:4) as eluent furnished the alcohol **10g** (10.5 g, 90%) as a viscous liquid

Rf = 0.3 (EtOAc-hexane 1:3); **IR** (neat): ν_{max}/cm^{-1} 3402 (OH), 2927, 2856, 1607, 1509, 1216, 1174, 1024, 756, 697, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.50-7.25 (m, 7H), 7.92 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 16.1 Hz, 1H), 6.2 (d, *J* = 16.1 Hz, 1H), 5.06 (s, 2H), 1.63(s, 1H), 1.41 (s, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 158.2, 136.9, 135.5, 129.8, 128.6, 127.9, 127.6, 127.5, 127.4, 125.7, 114.9, 71.03, 69.95, 29.87, 18.60; **HRMS-ESI**: m/z calcd for $C_{18}H_{20}O_2K$ [M+K$^+$]: 307.1463; found: 307.0933.

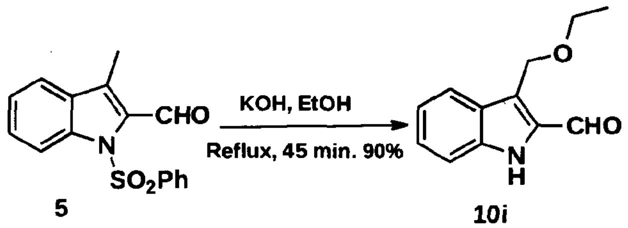
Example 16: Synthesis of compound 10h:



To a solution of the alcohol **10g** (4.0 g, 14.9 mmol) in anhydrous THF (40 ml) and Et_3N (2.4 ml, 89.6 mmol) under N_2 atm was added MsCl (3.5 ml, 44.7 mmol) slowly over a period of 5 min at -78 °C. The solution was allowed to warm to RT for 1.5 h and then refluxed for 30 min. The precipitate formed was filtered off using ethyl acetate affording a viscous liquid. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:19) as eluent furnished the diene **10h** (3.1 g, 83%) as a viscous liquid

Rf = 0.3 (EtOAc-hexane 1:19); **IR** (neat): ν_{max}/cm^{-1} 2975, 2400, 1601, 1509, 1239, 1216, 1025, 963, 668, 541; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.50-7.15 (m,7H), 7.92 (t of d *J* = 8.8 and 2.9 Hz, 2H), 6.76 (d, *J* = 16.1Hz, 1H), 6.46 (d, *J* = 16.1 Hz, 1H), 6.46 (d, *J* = 16.1 Hz, 1H), 5.10-4.98 (m, 4H), 1.95 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 158.4, 142.2, 137.0, 130.5, 129.9, 128.6, 128.2, 128.0, 127.7, 127.5, 116.4, 115.0, 70.0, 18.7; **HRMS-ESI**: *m/z* calcd for $C_{18}H_{18}O$ K [M+K$^+$]: 289.1358; found: 289.0661.

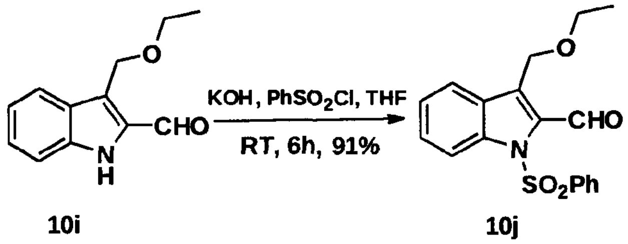
Example 17: Synthesis of compound 10i:



2-Formyl-3-methyl-l-phenylsulphonylindole **5** (5.0 g, 16.7 mmol) was added to powdered potassium hydroxide (4.7 g, 83.6 mmol) in ethanol (150 ml) and the mixture was stirred under reflux for 45 min and then concentrated under reduced pressure. Water (50 ml) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 50 ml), dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc-hexane (1:19) as eluent furnished the aldehyde **10i** (3.1 g, 90%) as a yellow solid

Rf = 0.35 (EtOAc-hexane 1:9). **IR** (neat): ν_{max}/cm^{-1} 2926, 2850, 2735, 1680 (C=O), 1462, 1365, 1174, 960, 724, 601; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 10.18 (s, 1H), 9.22 (s,1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.47-7.33 (m, 2H), 7.24-7.12 (m, 1H), 5.02 (s, 2H), 3.66 (q, *J* = 7.0 Hz, 2H), 1.28 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (50MHz, $CDCl_3$): δ 181.9, 137.2, 132.9, 127.5, 127.1, 124.2, 121.7, 121.1, 112.4, 66.2, 62.9, 15.3; **HRMS-ESI**: m/z calcd for $C_{12}H_{13}NO_2$ [M+H$^+$]: 204.0946; found: 204.0733.

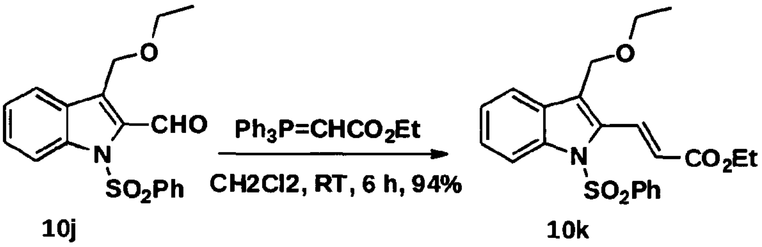
Example 18: Synthesis of compound 10j:



To a magnetically stirred solution of the indole **10i** (1.4 g, 6.86 mmol) in THF (15 ml) was added KOH powder (1.9 g, 34.3 mmol) followed by dropwise addition of $PhSO_2Cl$ (2.6 ml, 20.6 mmol) at 0 °C, and stirred magnetically for 6 h at RT. Water (20 ml) was then added to the reaction mixture, extracted with EtOAc (3 x 20 ml), washed with brine (20 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:9) as eluent furnished the compound **10j** (2.1 g, 91%) as white crystalline solid;

Rf = 0.3 (EtOAc -hexane 1:9); **IR** (neat): v_{max}/cm^{-1} 2974, 2926, 1677, 1543, 1372, 1175, 1088, 751, 724, 685; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 10.61 (s, 1H), 8.21 (t of d, *J* = 8.5 and 0.8 Hz, 1H), 7.97 (t of d, *J* = 8.0 and 1.0 Hz, 1H), 7.75-7.67 (m, 2H), 7.58-7.47 (m, 2H), 7.45-7.25 (m, 3H), 4.94 (s, 2H), 1.50 (q, *J* = 7.0 Hz, 2H), 1.20 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 153.3, 137.5, 137.1, 132.7, 126.3, 103.3, 70.9, 60.9, 56.0, 29.9; **HRMS-ESI**: m/z calcd for $C_{18}H_{17}NO_4S$ [M+H$^+$]: 344.0957; found: 344.0955.

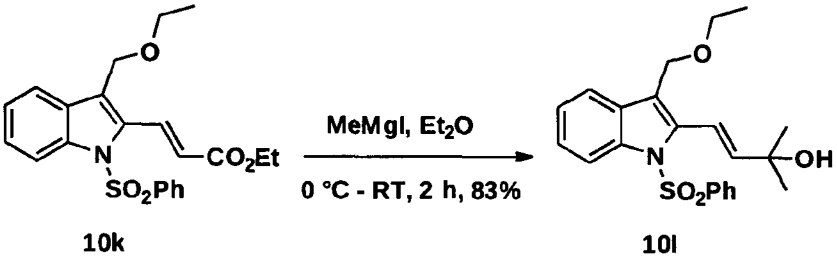
Example 19: Synthesis of compound 10k:



To a solution of the aldehyde **10j** (11 g, 32.1 mmol) in anhydrous CH_2Cl_2 (200 ml) was added dry $Ph_3P=CHCO_2Et$ (16.8 g, 48.2 mmol) and stirred magnetically for 6 h at RT. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (2:8) as eluent gave the ester **10k** (12.5 g, 94 %) as white crystalline solid

Rf = 0.35 (EtOAc-hexane 3:7); **IR** (neat): v_{max}/cm^{-1} 3019, 1708 (OC=O), 1630, 1448, 1374, 1215, 758, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.30-8.15 (m, 2H), 7.80-7.60 (m, 3H), 7.55-7.20 (m, 5H), 6.30 (d, *J* = 15.9 Hz, 1H), 4.55 (s, 2H) 4.33 (q, *J* = 7.1 Hz, 2H), 3.51 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (50 MHz, CD_3CN): δ 175.4, 175.1, 162.6, 147.8, 130.2, 129.7, 116.5, 95.7, 81.8, 81.1, 69.9, 69.4, 67.3, 67.2, 67.1, 66.7, 66.6, 60.3, 52.8, 52.7, 40.7, 40.1, 28.5, 27.7, 26.8, 24.5, 23.4; **HRMS-ESI:** calcd for $C_{22}H_{23}NO_5SNa$ [M+Na$^+$] 436.1195; found: 436.1194.

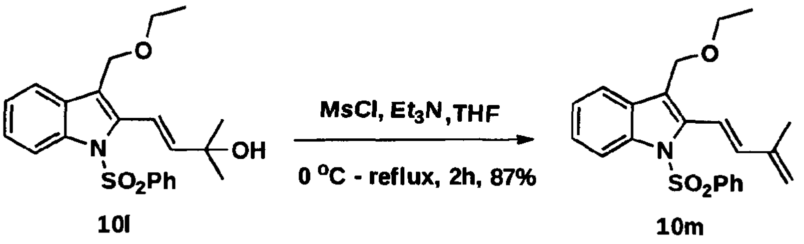
Example 20: Synthesis of compound 10l:



To a cold (0 °C), magnetically stirred solution of the ester **10k** (10.0 g, 24.2 mmol) was added methyl magnesium iodide [prepared from magnesium turnings (2.6 g, 72.6 mmol), methyl iodide (10.1 ml, 96.8 mmol) and few crystals of iodine in anhydrous ether (75 ml)] and stirred for 2 h at RT. The reaction mixture was then quenched with aq.NH_4Cl solution (50 ml) and worked up. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (2:8) as eluent furnished the tertiary alcohol **10l** (8.0 g, 83%) as a waxy solid;

Rf = 0.3 (EtOAc-hexane 2:3); **IR** (neat): ν_{max}/cm^{-1} 2853, 1583, 1455, 1170, 963, 725, 595; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.20 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.74 (d, *J* = 7.3Hz, 2H), 7.65-7.15 (m, 6H), 7.02 (d, *J* = 16.0, 1H), 4.48 (s, 2H), 3.48 (q, *J* = 7.0 Hz, 2H), 1.48 (s, 6H), 1.18 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 146.2, 138.4, 137.3, 136.1, 133.8, 130.4, 129.0, 126.7, 125.0, 123.9, 119.7, 1189.4, 116.0, 114.6, 71.1, 65.6, 29.7, 15.2; **HRMS-ESI:** calcd for $C_{22}H_{25}NO_4SNa$ [M+Na^+] 422.1402; found: 422.1393.

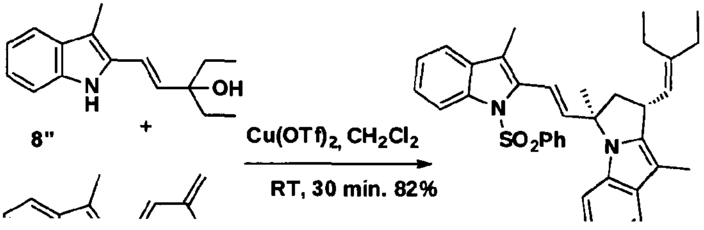
Example 21: Synthesis of compound 10m:



To a solution of alcohol **10l** (6.0 g, 15.0 mmol) in anhydrous THF (40 ml) and Et_3N (12.5 ml, 90.0 mmol) under N_2 atmosphere was added MsCl (3.5 ml, 45.0 mmol) slowly over a period of 4 min at 0°C .The solution was allowed to warm at RT for 1.5 h and then refluxed for 30 min. The precipitate formed was filtered off using ethyl acetate affording a brown viscous liquid. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:19) as eluent furnished the diene **10m** (5.0 g, 87%) as a white solid

Rf = 0.40 (EtOAc-hexane 1:9); **IR** (neat): ν_{max}/cm^{-1} 3019, 1646, 1449, 1363, 1216, 1088, 586; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.2 Hz, 1H), 7.80-7.53 (m, 3H), 7.50-7.16 (m, 5H), 7.05 (d, *J* = 16.1 Hz, 1H), 6.61 (d, *J* = 16.1 Hz, 1H), 5.17 (d, *J* = 5.6 Hz, 2H), 4.51 (s, 2H), 3.50 (q, *J* = 7.0, 2H), 2.07 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 142.1, 139.0, 138.3, 138.1, 136.3, 133.8, 130.7, 129.0, 126.8, 125.1, 124.0, 119.7, 119.1, 118.7, 118.2, 114.8, 65.7, 63.5, 18.5, 15.3; **HRMS-ESI:** Calcd for $C_{22}H_{23}NO_3SNa$ [M+Na^+] 404.1296; Found: 404.1296.

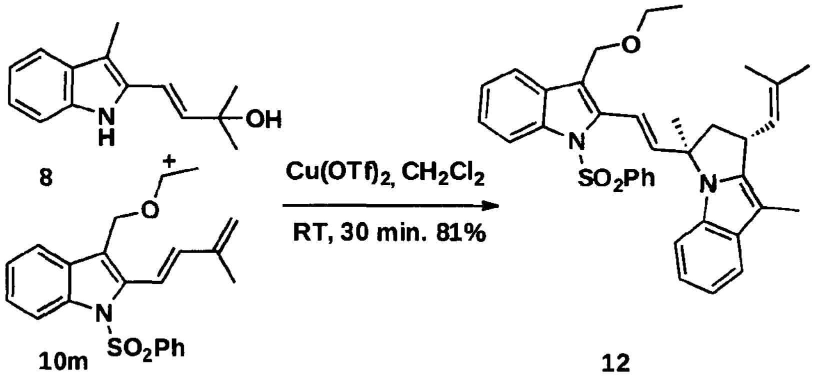
Example 22: Synthesis of compound 11:



To a solution of the alcohol **8''** (40 mg, 0.16 mmol) and diene **7** (55 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (5 ml) was added a catalytic amount of $Cu(OTf)_2$ (11 mg, 0.03 mmol) and stirred magnetically for 0.5 h at RT. The progress of reaction was monitored by TLC till the starting alcohol had been completely consumed. Water (10 ml) was then added to the reaction mixture, extracted with CH_2Cl_2 (3 x 5 ml), washed with brine (5 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:49) as eluent furnished the isomer **11** (76 mg, 82 %) as white crystalline solid

Rf = 0.4 (EtOAc-hexane 1:49); **IR** (neat): ν_{max}/cm^{-1} 2970, 1641, 1454, 1371, 1215, 1022, 668; ^{1}**H NMR** (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.4 Hz, 1H), 7.59 (t, *J* = 4.4 Hz, 1H), 7.46 (t, *J* = 4.1 Hz, 1H), 7.39-7.18 (m, 5H), 7.11-7.06 (m, 2H), 7.02 (t, *J* = 7.9 Hz, 2H), 6.35 (d, *J* = 16.1 Hz, 1H), 5.99 (d, *J* = 16.1 Hz, 1H), 5.26 (d, *J* = 9.5 Hz, 1H), 4.40 (q, *J* = 8.8 Hz, 1H), 2.83 (dd, *J* = 12.6 and 7.7 Hz, 1H), 2.40-2.26 (m, 2H), 2.24 (s, 3H), 2.21-2.09 (m, 6H), 2.02 (s, 3H), 1.07 (t, *J* = 7.5 Hz, 3H), 1.06 (t, *J* = 7.5 Hz, 3H); ^{13}**C NMR** (125 MHz, $CDCl_3$): δ 144.9, 142.9, 139.4, 138.3, 136.1, 133.8, 133.3, 131.6, 131.4, 128.9, 126.5, 124.9, 123.6, 122.7, 120.3, 119.0, 118.6, 118.5, 117.9, 114.9, 109.9, 101.9, 63.7, 51.7, 34.4, 29.2, 25.5, 23.7, 13.7, 12.9, 10.2, 7.9; **HRMS-ESI**: m/z calcd for $C_{19}H_{17}NO_5S$ [M+H$^+$]: 563.2732; found: 563.2736.

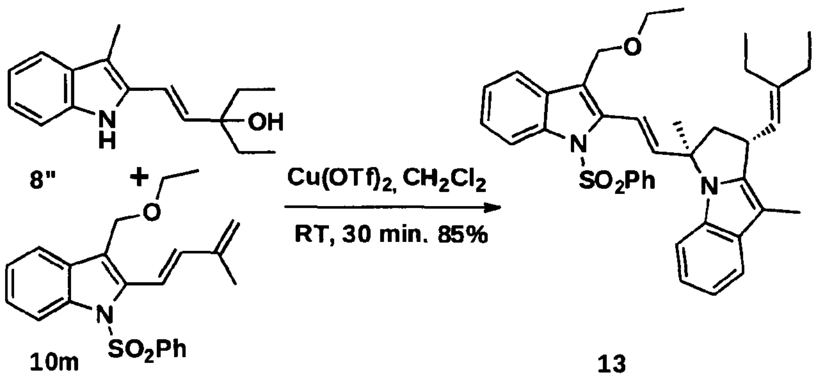
Example 23: Synthesis of compound 12:



To a solution of the alcohol **8** (40 mg, 0.186 mmol) and diene **10m** (68 mg, 0.204 mmol) in anhydrous CH_2Cl_2 (5 ml) was added a catalytic amount of $Cu(OTf)_2$ (11 mg, 0.03 mmol) and stirred magnetically for 0.5 h at RT. The progress of reaction was monitored by TLC till the starting alcohol had been completely consumed. Water (5 ml) was then added to the reaction mixture, extracted with CH_2Cl_2 (3 x 5 ml), washed with brine (5 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:19) as eluent furnished the isomer **12** (86 mg, 81 %) as white crystalline solid

Rf = 0.4 (EtOAc-hexane 1:19); **IR** (neat): ν_{max}/cm^{-1} 2977, 1450, 1377, 1174, 1089, 929, 669; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 8.17 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.60-7.48 (m, 2H), 7.45-7.16 (m, 6H), 7.14-7.00 (m, 4H), 6.37 (d, *J* = 15.8 Hz 1H), 6.17 (d, *J* = 15.9 Hz, 1H), 5.30 (septet of a doublet, *J* = 9.5 and 1.3 Hz, 1H), 4.38 (d, *J* = 2.1 Hz, 2 H), 4.45-4.25 (m, 1 H), 3.45-3.20 (m, 2 H), 2.80 (dd, *J* = 12.5 and 7.5 Hz, 1H), 3.45-3.20 (m, 2 H), 2.80 (dd, *J* = 12.5 and 7.5 Hz, 1H), 2.33 (dd, *J* = 12.6 and 9.6 Hz,), 2.03 (s, 3H), 1.82 (s, 6H), 1.12 (t, *J* = 7.0 Hz, 3H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 142.0, 140.7, 138.4, 136.7, 135.9, 129.7, 116.5, 133.9, 133.7, 133.6, 131.55, 130.2, 129.0, 126.5, 125.0, 124.6, 123.7, 120.3 119.5, 118.6, 118.2, 117.5, 114.5, 110.0, 102.0, 65.6, 63.6, 63.3, 51.2, 34.8, 25.7, 25.4, 18.2, 15.2, 7.8; **HRMS**-ESI: calcd for $C_{36}H_{38}N_2O_3S$ [M+H$^+$] 579.2681; found: 579.2695.

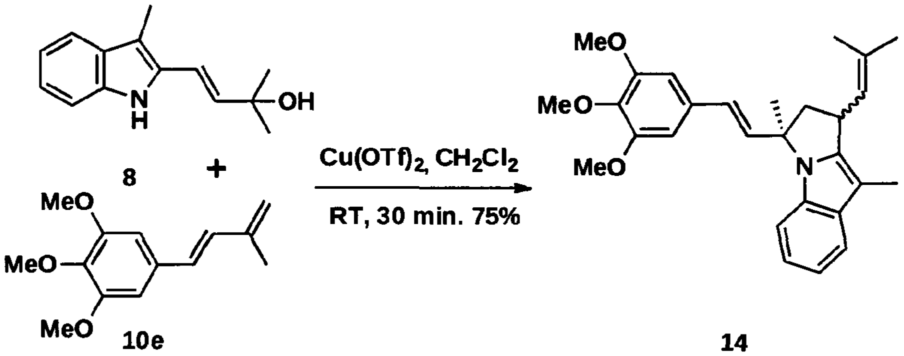
Example 24: Synthesis of compound 13:



To a solution of the alcohol **8''** (50 mg, 0.205 mmol) and diene **10m** (69 mg, 0.205 mmol) in anhydrous CH_2Cl_2 (5 ml) was added a catalytic amount of $Cu(OTf)_2$ (15 mg, 0.04 mmol) and stirred magnetically for 0.5 h at RT. The progress of reaction was monitored by TLC till the starting alcohol had been completely consumed. Water (5 ml) was then added to the reaction mixture, extracted with CH_2Cl_2 (3 x 5 ml), washed with brine (5 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:19) as eluent furnished the isomer **13** (106 mg, 85 %) as white crystalline solid

Rf = 0.4 (EtOAc-hexane 1:19); **IR** (neat): v_{max}/cm^{-1} 2975, 1449, 1046, 929, 669; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 8.17 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.60-7.49 (m, 2H), 7.45-7.16 (m, 6H), 7.14-7.00 (m, 4 H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.18 (d, *J* = 15.7 Hz, 1H), 5.26 (d, *J* = 9.6 Hz, 1H), 4.38 (d, *J* = 2.9 ,2H), 4.45-4.25 (m, 1 H), 3.60-3.17 (m, 2H), 2.79 (dd, *J* = 12.5 and 7.5 Hz, 1H), 2.45-2.09 (m, 9H), 2.04 (s,3H), 1.12 (t, *J* = 7.0 Hz), 2.80 (dd, *J* = 12.5, 7.5 Hz, 1H), 2.33 (dd, *J* = 12.6, 9.6 Hz), 2.03(s, 3H), 1.82 (s, 6H), 1.12 (t, *J* = 7.0 Hz, 3H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 144.9, 142.7, 140.7, 138.4, 136.8, 135.9, 133.8, 133.5, 131.5, 130.2, 129.0, 126.5, 125.0, 123.7, 122.6, 120.4, 119.5, 118.6, 118.2, 117.6, 114.5, 110.0, 102.12, 65.6, 63.3, 51.7, 34.4, 29.125.3, 23.7, 15.2, 13.7, 12.9, 7.9; **HRMS** (ESI) m/z calcd for $C_{38}H_{42}N_2O_3S$ [M+H$^+$]: 607.2994; found: 607.2994.

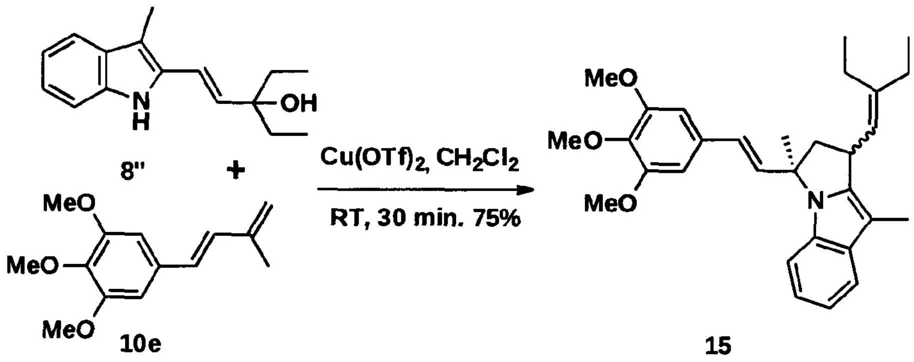
Example 25: Synthesis of compound 14



To a solution of the alcohol **8** (40 mg, 0.19 mmol) and diene **10e** (43 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (5 ml) was added a catalytic amount of $Cu(OTf)_2$ (11 mg, 0.03 mmol) and stirred magnetically for 0.5 h at RT. The progress of reaction was monitored by TLC till the starting alcohol had been completely consumed. Water (5 ml) was then added to the reaction mixture, extracted with CH_2Cl_2 (3 x 5 ml), washed with brine (5 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:4) as eluent furnished the mixture of isomer **14** (64 mg, 75 %) as colourless oil;

Rf = 0.4 (EtOAc-hexane 1:4); **IR** (neat): v_{max}/cm^{-1} 2924, 1585, 1420, 1129, 1044, 929, 669; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 7.60-7.42 (m, 1H), 7.35-7.20 (m, 1H), 7.17-6.92 (m, 2H), 6.63 (s, 0.72H), 6.54 (s, 0.28H), 6.50 (s,1.16H), 6.45 ((d, *J* = 16.1 Hz, 0.46H), 6.31 (d, *J* = 16.1 Hz, 0.63H), 5.90 (d *J* = 16.1Hz, 0.63H), 5.27 (d, *J* = 9.4Hz, 1H), 4.00-4.35 (m, 1H), 3.85 (s, 3H), 3.82 (d, *J* = 3.2 Hz,6H), 2.85-2.50 (m, 1H), 2.45-2.23 (m, 1H), 2.20 (dd, *J* = 1.0 Hz, 3H), 1.90 (s, 2H), 1.80 (s, 6H), 1.58 (s, 1H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 153.4, 153.3, 142.7, 142.1, 137.9, 137.7, 134.2, 133.6, 133.5, 133.2, 133.0, 132.8, 132.3, 132.2, 131.4, 131.2, 129.1, 127.6, 124.9, 124.8, 120.2, 118.4, 118.3, 110.0, 109.9, 103.5, 103.5, 101.7, 101.5, 63.5, 62.6, 60.9, 56.1, 52.1, 51.9, 35.2, 34.7, 26.2, 25.7, 23.0, 18.2, 7.8; **HRMS-ESI**: calcd for $C_{28}H_{33}NO_3$ [M+H$^+$] 432.2539; found: 432.2529.

Example 26: Synthesis of compound 15



8''

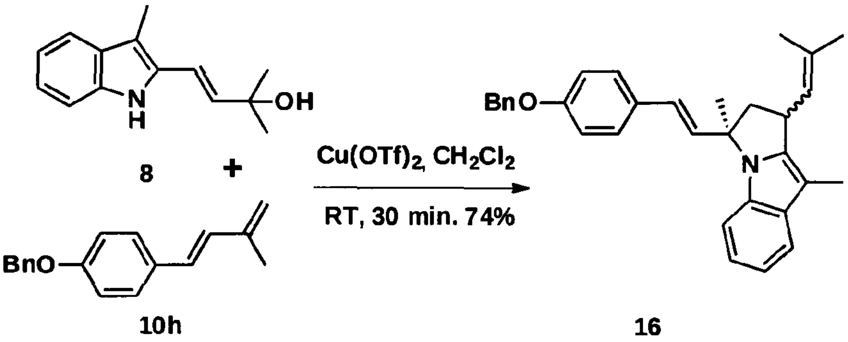
10e

15

To a solution of the alcohol **8''** (57 mg, 0.23 mmol) and diene **10e** (55 mg, 0.23 mmol) in anhydrous CH_2Cl_2 (5 ml) was added a catalytic amount of $Cu(OTf)_2$ (15 mg, 0.04 mmol) and stirred magnetically for 0.5 h at RT. The progress of reaction was monitored by TLC till the starting alcohol had been completely consumed. Water (5 ml) was then added to the reaction mixture, extracted with CH_2Cl_2 (3 x 5 ml), washed with brine (5 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:9) as eluent furnished the mixture of isomers **15** (81 mg, 75 %) as colourless oil

Rf = 0.35 (EtOAc-hexane 1:9); **IR** (neat): ν_{max}/cm^{-1} 2965, 2934, 2875, 1582, 1454, 1340, 1242, 1127, 1009, 813, 665; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 7.60-7.42 (m, 1H), 7.35-7.20 (m, 1H), 7.17-6.92 (m, 2H), 6.63 (s, 0. 2H), 6.54 (s, 0.28H), 6.50 (s, 1.06H), 6.45 (d, *J* = 16.1 Hz, 0.46H), 6.33 (d, *J* = 16.1 Hz, 0.63 H), 5.90 (d, *J* = 16.1 Hz, 0.63H), 5.23 (d, *J* = 9.7Hz, 1H), 4.35-4.00 (m, 1H), 3.85 (s, 3H), 3.82 (d, *J* = 3.5 Hz, 6H), 2.75 (d, *J* = 12.5, 7.8 Hz, 0.6H), 2.60 (d, *J* = 12.5, 7.8 Hz, 0.40H), 2.50-2.00 (m, 8H), 1.90 (s, 1.8H), 1.65 (dd, *J* = 18.8 Hz, 1.8H), 1.15-0.98 (m, 6H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 153.4, 153.3, 144.4, 144.2, 142.8, 142.1, 137.8, 137.7, 134.2, 133.6, 133.5, 132.8, 132.3, 132.2, 131.4, 131.1, 129.1, 127.5, 123.0, 122.9, 120.2, 118.4, 118.3, 110.1, 109.9, 103.5, 103.4, 101.8, 101.6, 63.5, 62.6, 60.9, 56.1, 56.1, 52.6, 52.3, 34.8, 34.2, 29.1, 26.3, 23.6, 22.9, 13.6, 12.9, 7.9; **HRMS-ESI:** calcd for $C_{30}H_{37}NO_3$ [M+H$^+$] 460.2852; found: 460.2842.

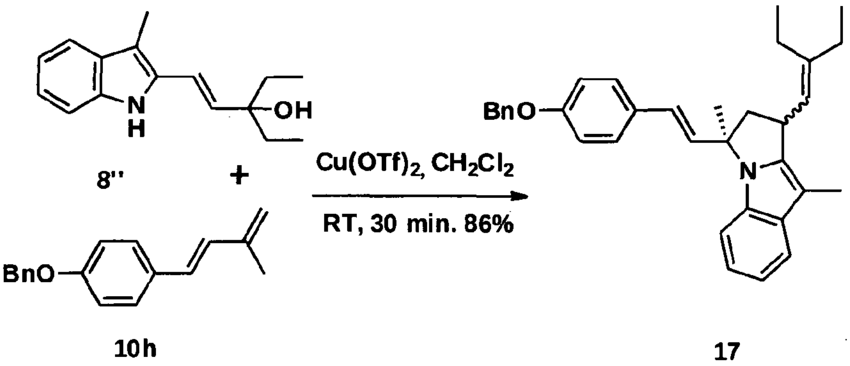
Example 27: Synthesis of compound 16



To a solution of the alcohol **8** (50 mg, 0.23 mmol) and diene **10h** (58 mg 0.23 mmol) in anhydrous CH_2Cl_2 (5 ml) was added a catalytic amount of $Cu(OTf)_2$ (15 mg, 0.04 mmol) and stirred magnetically for 0.5 h at RT. The progress of reaction was monitored by TLC till the starting alcohol had been completely consumed. Water (5 ml) was then added to the reaction mixture, extracted with CH_2Cl_2 (3 x 5 ml), washed with brine (5 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:49) as eluent furnished the mixture of isomers **16** (60 mg, 74 %) as white crystalline solid;

Rf = 0.3 (EtOAc-hexane 1:49). **IR** (neat): ν_{max}/cm^{-1} 2972, 2928, 1880, 1606, 1509, 1454, 1174, 1013, 697, 667; **^{1}H NMR (200 MHz, CDCl$_3$):** δ 7.55-7.45 (m, 1H), 7.44-7.15 (m, 8H), 7.10-6.80 (m, 4H), 6.59 (d, *J* = 16.1 Hz, 0.36H), 6.39 (d, *J* = 16.1 Hz, 0.36H), 6.24 (d, *J* = 16.1 Hz, 0.64H), 5.91 (d, *J* = 16.1 Hz, 0.64H), 5.26 (d, *J* = 9.5 Hz, 1H), 5.04(d, *J* = 7.2 Hz, 2 H), 4.15 (septet, *J* = 7.6 Hz, 1H), 2.73 (dd, *J* = 12.6 and 7.8 Hz, 0.64H), 2.60 (dd, *J* = 12.6, 7.8 Hz, 0.36H), 2.40-2.1 (m, 4H), 1.87 (s, 2H), 1.79 (s, 6H), 1.65 (s, 1H); **^{13}C NMR (50 MHz, CDCl$_3$):** δ 158.5, 158.3, 142.7, 142.1, 136.9, 133.6, 133.6, 133.1, 132.8, 132.7, 131.5, 131.3, 131.2, 129.7, 129.5, 128.6, 128.0, 127.7, 127.4, 127.1, 125.1, 125.0, 120.1, 118.4, 118.3, 118.2, 115.0, 114.9, 110.0, 101.5, 70.0, 63.5, 62.7, 52.0, 51.9, 35.2, 34.7, 26.1, 25.7, 23.1, 18.2, 7.8; **HRMS-ESI**: m/z calcd for $C_{32}H_{33}NONa$ [M+Na$^+$]: 470.2460; found: 470.2463.

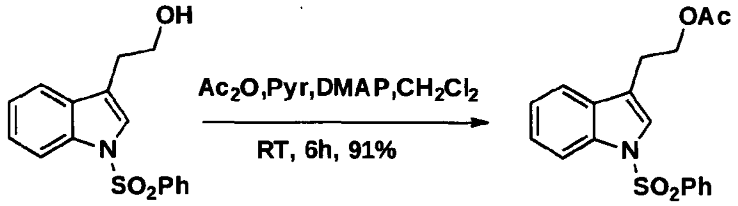
Example 28: Synthesis of compound 17



To a solution of the alcohol **8''** (40 mg, 0.164 mmol) and diene **10h** (41 mg, 0.164 mmol) in anhydrous CH_2Cl_2 (5 ml) was added a catalytic amount of $Cu(OTf)_2$ (11 mg, 0.03 mmol) and stirred magnetically for 0.5 h at RT. The progress of reaction was monitored by TLC till the starting alcohol had been completely consumed. Water (5 ml) was then added to the reaction mixture, extracted with CH_2Cl_2 (3 x 5 ml), washed with brine (5 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:49) as eluent furnished the mixture of isomer **17** (66 mg, 86 %) as white crystalline solid

Rf = 0.4 (EtOAc-hexane 1:49); **IR** (neat): v_{max}/cm^{-1} 3020, 1648, 1444, 1049, 668, 967, 787, 603; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 7.55-7.45 (m, 1H), 7.44-7.15 (m, 8H), 7.10-6.80 (m, 4H), 6.61 (d, *J* = 16.1 Hz, 0.36H), 6.40 (d, *J* = 16.1 Hz, 0.36 H), 6.25 (d, *J* = 16.1 Hz, 0.64H), 5.91 (d, *J* = 16.1Hz, 0.64H), 5.22 (d, *J* = 9.5 Hz,1H), 5.04 (d, *J* = 7.2 Hz, 2H), 4.20 (septet, *J* = 7.6 Hz, 1H), 2.72 (dd, *J* = 12.6, 7.8 Hz, 0.64H), 2.58 (dd, *J* = 12.6, 7.8 Hz, 0.36H), 2.40-2.00 (m, 8 H), 1.88 (s, 2H), 1.66 (s, 1H), 1.15-0.95 (m, 6H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 158.5, 158.3, 144.3, 144.1, 142.8, 136.9, 133.6, 133.5, 132.7, 131.5, 131.3, 131.2, 129.7, 129.5, 128.6, 128.0, 127.7, 127.4, 127.0, 123.1, 120.1, 118.4, 118.3, 118.2, 115.0, 114.9, 110.0, 109.9, 101.6, 101.5, 70.0, 63.5, 62.7, 52.4, 52.3, 34.8, 34.2, 29.1, 26.2, 23.5, 23.0, 13.6, 12.9, 7.9; **HRMS-ESI**: m/z calcd for $C_{34}H_{37}NO$ [M-H$^-$]: 474.2875; found: 474.2701.

Example 29: Synthesis of compound 21

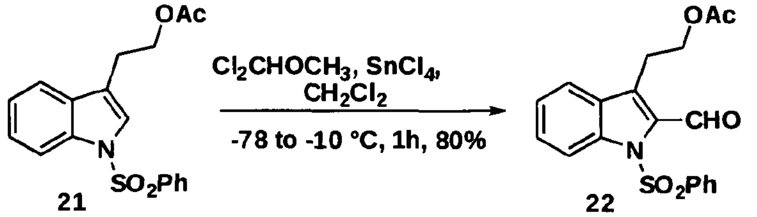


20 21

To a magnetically stirred solution of the N-protected tryptophol **20** (25 g, 83.05 mmol) in CH_2Cl_2 (200 ml) was added pyridine (36.45 ml, 415.3 mmol), Ac_2O (39.2 ml, 415.3 mmol) and DMAP (2 g, 16.6 mmol). The reaction mixture was stirred for 6 h at RT and extracted with CH_2Cl_2, washed with brine, dil.HCl and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using EtOAc-hexane (1:4) as eluent furnished the compound **21** (16 g, 91%) as white crystalline solid

Rf = 0.4 (EtOAc-hexane 1:4); **IR** (neat): v_{max}/cm^{-1} 2958, 1736, 1448, 1176 (O-C=O), 787,571; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 8.02-7.84 (m, 3H), 7.57-7.06 (m, 7H), 4.32 (t, *J* = 6.95, 2H), 3.0 (t, *J* = 6.95, 2H), 2.03 (s, 3H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 170.9, 138.1, 135.1, 133.7, 130.7, 129.2, 126.6, 124.8, 123.4, 123.2, 119.3, 118.9, 113.6, 63.1, 24.4, 20.9; **HRMS**-ESI: calcd for $C_{18}H_{17}NO_4S$ [M+Na$^+$] 366.0776; found: 366.0759.

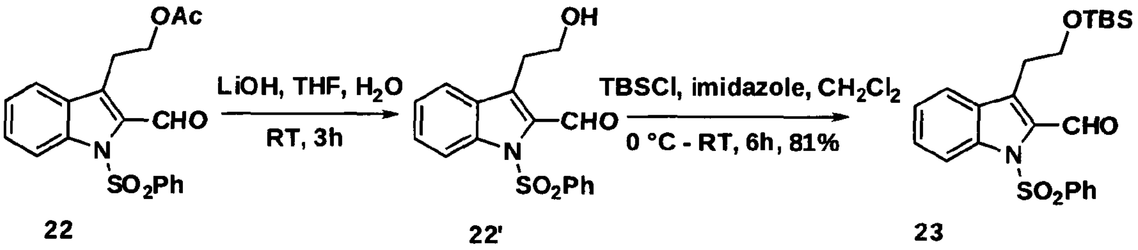
Example 30: Synthesis of compound 22



To a cold (-78 °C), magnetically stirred solution of the indole **21** (30 g, 87.5 mmol) in CH_2Cl_2 (200 ml) was added $MeOCHCl_2$ (38.8 ml, 437.3 mmol) and $SnCl_4$ (51.2 ml, 437.3 mmol). The reaction mixture was allowed to come to -10 °C slowly over a period of 1 h and was poured into HCl (1*M* 500 ml). It was then extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4. Evaporation of the solvent and recrystallisation of the crude product from 1,2-dichloroethane furnished the aldehyde **22** (26 g, 80%) as a white solid.

Rf = 0.4 (EtOAc-hexane 2:8); **IR** (neat): ν_{max}/cm^{-1} 2923, 2853, 1738 (O-C=O), 1675 (C=O), 1543, 1448, 1175, 904, 724; ^{1}**H NMR** ($CDCl_3$, 200 MHz): δ 10.6 (s, 1H), 8.2 (d, *J* = 8.5 Hz, 1H), 7.75-7.25 (m, 8H), 4.26 (t, *J* = 6.7 Hz, 2H), 3.30 (t, *J* = 6.7 Hz, 2H), 1.83 (s, 3H); ^{13}**C NMR** ($CDCl_3$, 50MHz): δ 184.5, 170.5, 137.2, 136.5, 134.0, 133.2, 132.0, 130.0, 129.1, 128.9, 126.3, 124.7, 121.5, 115.6, 60.3, 24.2, 20.5; **HRMS**: m/z calcd for $C_{19}H_{17}NO_5SNa$ [$M+Na^+$]: 394.0725; found: 394.0725.

Example 31: Synthesis of compound 23

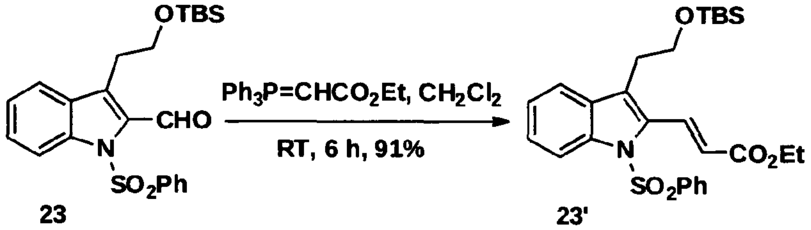


To a solution of the acetate **22** (15 g, 40.4 mmol) in THF (600 ml) was added a solution of LiOH (4.6 g, 202.2 mmol) in water (150 ml) and stirred magnetically for 3 h at RT. The reaction mixture was extracted with ethyl acetate, washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude alcohol **22'** which was used in next step without further purification. To a cold (0 °C) solution of the crude alcohol **22'** (12 g, 36.5 mmol) in CH_2Cl_2 (200 ml) was added imidazole (3.7 g, 54.7 mmol), TBSCl (7.1 g, 47.4 mmol) at 0°C and stirred magnetically for 6 h at RT. It was then extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using

EtOAc-hexane (1:19) as eluent furnished the compound **23** (16 g, 81%, over 2 steps) as a white crystalline solid;

Rf = 0.4 (EtOAc-hexane 1:19); **IR** (neat): v_{max}/cm^{-1} 2928, 1674 (C=O), 1448, 1368, 1174, 1089, 753, 595; ^{1}**H NMR** (CD_3CN, 200 MHz): δ 10.46 (s, 1H), 8.1 (dt, *J* = 8.5 and 0.8 Hz, 1H), 7.75-7.20 (m, 8H), 3.75 (t, *J* = 6.2 Hz, 2H), 3.08 (t, *J* = 6.2 Hz, 2H), 0.86 (s, 9H), -0.24 (s, 6H); ^{13}**C NMR** (CD_3CN): δ 183.8, 136.7, 136.1, 134.1, 133.6, 128.9, 128.7, 126.2, 124.2, 122.3, 116.8, 114.9, 62.3, 27.6, 24.7, -4.6, -6.7.

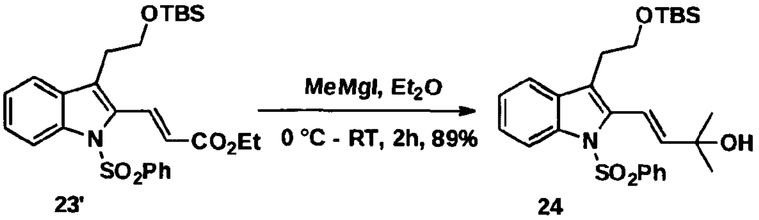
Example 32: Synthesis of compound 23'



To a stirred solution of the aldehyde **23** (15 g, 33.9 mmol) in CH_2Cl_2 (150 ml) was added stabilised two carbon Wittig salt (17.7 g, 50.8 mmol) [prepared from Ph_3P (50 g, 190.0 mmol), ethyl bromoacetate (21.1 ml, 190.0 mmol) and toluene (300 ml)]. The reaction mixture was stirred for 6 h at RT. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using EtOAc-hexane (1:19) as eluent furnished the ester **23'** (16 g, 91%) as white crystalline solid;

Rf = 0.5 (EtOAc-hexane 1:9); **IR** (neat): v_{max}/cm^{-1} 2929, 2856, 1711 (O-C=O), 1630, 1174, 751, 577; ^{1}**H NMR** ($CDCl_3$, 200 MHz): δ 8.37-7.29 (m, 10H), 6.52 (d, *J* = 16Hz, 1H), 4.39 (q, *J* = 14.3, 7.2 Hz, 2H), 3.91 (t, *J* = 6.2 Hz, 2H), 3.04 (t, *J* = 6.4 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H), 0.85 (s, 9H), -0.1 (s, 6H); ^{13}**C NMR** ($CDCl_3$, 50MHz): δ 166.3, 137.8, 137.0, 133.8, 133.7, 132.9, 130.8, 128.9, 126.6, 126.2, 124.5, 123.9, 122.5, 120.1, 115.2, 62.6, 60.6, 28.5, 25.8, 18.1, 14.2, -5.6; **HRMS**: m/z calcd for $C_{27}H_{35}NO_5SSi$ Na [M+Na$^+$]: 536.1903; found: 536.1909.

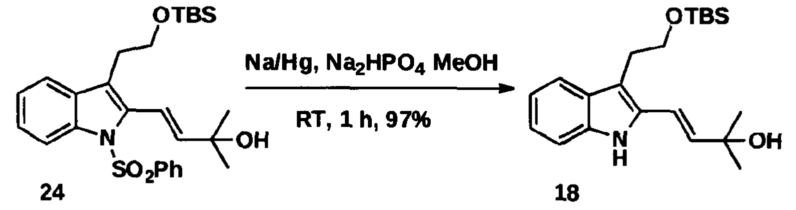
Example 33: Synthesis of compound 24



To a magnetically stirred solution of methylmagnesium iodide, [prepared from magnesium turnings (6.4 g, 29.2 mmol), methyl iodide (18.2 ml, 292.4 mmol) and few crystals of iodine in anhydrous ether (50 ml)] was added slowly a mixture of the ester **23'** (15 g, 269.1 mmol) in anhydrous ether (50 ml). The reaction mixture was stirred for 2 h at RT. It was then quenched with aq. NH_4Cl solution (50 ml), extracted with ethyl acetate (3 x 15 ml), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc-hexane (3:7) as eluent furnished the alcohol **24** (13 g, 89%) as a white solid;

Rf = 0.35 (EtOAc-hexane 1:3); **IR** (neat): v_{max}/cm^{-1} 3547 (OH), 2927, 1449, 1356, 1109, 751, 577; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 8.35 (dt, *J* = 8.3 Hz, 1.1Hz, 1H), 7.84 (dt, *J* = 7.1, 1.5 Hz, 2H), 7.64-7.28 (m, 6H), 7.06 (d, *J* = 16.2 Hz, 1H), 6.28 (d, *J* = 16.2 Hz, 1H), 3.91 (t, *J* = 6.7 Hz, 2H), 3.01 (t, *J* = 6.8 Hz, 2H), 1.63 (s, 6H), 0.9 (s, 9H), -0.05 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 144.1, 138.3, 136.1, 135.0, 133.4, 131.1, 128.7, 126.5, 124.7, 123.5, 119.4, 116.5, 114.8, 71.0, 62.7, 29.6, 28.4, 25.8, 18.1, 5.5; **HRMS**: m/z calcd for $C_{27}H_{37}NO_4SSiNa$ [M+Na$^+$]: 522.2110; found: 522.2100.

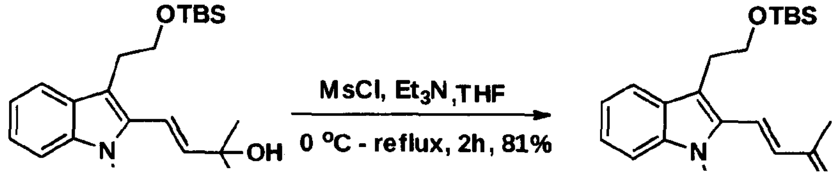
Example 34: Synthesis of compound 18



To a mixture of the compound **24** (5 g, 10 mmol) in anhydrous methanol (50 ml) was added Na_2HPO_4 (5.7 g, 40.2 mmol) and Na-Hg (9.2 g, 40.2 mmol). The reaction mixture was stirred for 1 h at RT until all the amalgam had converted into liquid mercury. Water (20 ml) was added to the reaction mixture, extracted with ether (3 x 15 ml), washed with brine (20 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc-hexane (3:7) as eluent furnished the alcohol **18** (3.5 g, 97%) as a yellow solid;

Rf = 0.3 (EtOAc-hexane 3:7); **IR** (neat): v_{max}/cm^{-1} 3455 (OH), 3361 (NH), 3058, 2929, 1462, 1255, 1092,793; **^{1}H NMR** (CD_3CN, 400 MHz): δ 9.11 (br s, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 8 Hz, 1H), 6.97 (t, *J* = 7 Hz, 1H), 6.86 (t, *J* = 7.3 Hz, 1H), 6.56 (d, *J* = 16.3 Hz, 1H), 6.12 (d, *J* = 16.3 Hz, 1H), 3.66 (t, *J* = 7 Hz, 2H), 2.84 (t, *J* = 7 Hz, 2H), 2.80 (br s, 1H), 1.23 (s, 6H), 0.71 (s, 9H), -0.18 (s, 6H); **^{13}C NMR** (CD_3CN, 50 MHz): δ 136.4, 136.1, 132.8, 128.5, 121.8, 118.5, 118.2, 116.9, 114.5, 111.0, 110.1, 69.7, 63.1, 29.0, 27.2, 25.0, 17.6, 6.4; **HRMS**: m/z calcd for $C_{21}H_{33}NO_2SiK$ [M+K$^+$]: 398.1918; found: 398.1931.

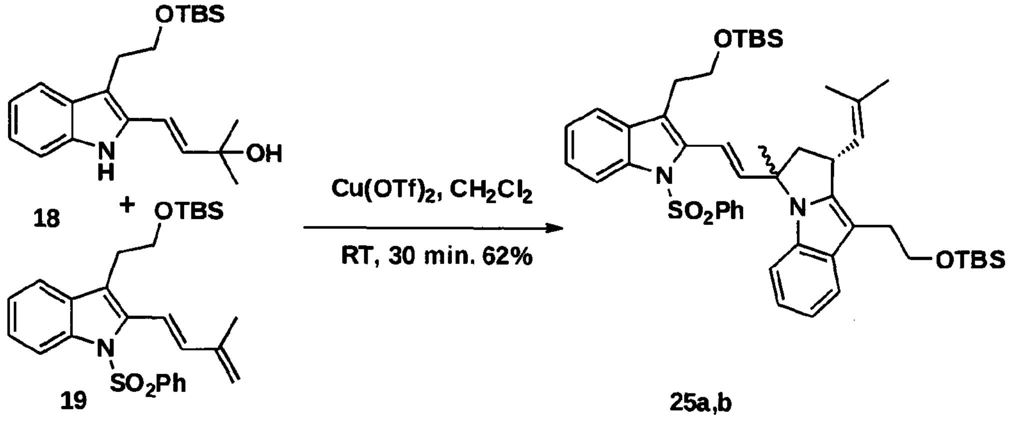
Example 35: Synthesis of compound 19



To a cold (-78 °C), magnetically stirred solution of the alcohol **24** (5 g, 10 mmol) and dry Et_3N (8.3 ml, 60.24 mmol) in anhydrous THF (50 ml) was added MsCl (2 ml, 26 mmol). The reaction mixture was slowly allowed to warm to RT for 1.5 h and refluxed for 30 min. The precipitate formed was filtered using ethyl acetate. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc-hexane (1:19) as eluent furnished the diene **19** (4.7 g, 81%) as a white crystalline solid;

Rf = 0.5 (EtOAc-hexane 1:19); **IR** (neat): ν_{max}/cm^{-1} 3068, 2954, 2857, 1603, 1449, 1376, 1173, 1091, 748, 579; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 8.23 (dt, *J* = 8.2, 1.01 Hz, 1H), 7.71-7.16 (m, 8H), 6.98 (d, *J* = 16.2 Hz, 1H), 6.62 (d, *J* = 16.3 Hz, 1H), 5.14 (d, *J* = 5.9 Hz, 2H), 3.8 (t, *J* = 6.8 Hz, 2H), 2.93 (t, *J* = 6.9 Hz, 2H), 2.07 (s, 3H), 0.78 (s, 9H), -0.17 (s, 6H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 142.1, 138.3, 137.0, 136.4, 135.7, 133.4, 131.3, 128.8, 126.6, 124.8, 123.6, 119.6, 119.4, 118.9, 118.3, 115.1, 62.7, 28.6, 25.8, 18.5, 18.2, -5.5; **HRMS**: m/z calcd for $C_{27}H_{35}NO_3SSi$ [M+H$^+$]: 482.2185; found: 482.2178.

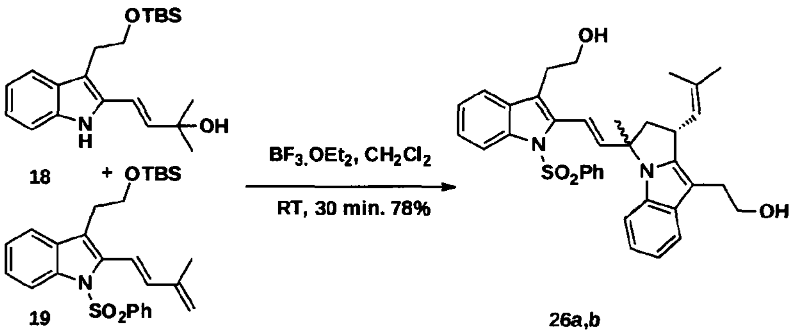
Example 36: Synthesis of compound 25a and 25b



To a solution of the alcohol **18** (200 mg, 0.55 mmol) and diene **19** (268 mg, 0.55 mmol) in anhydrous CH_2Cl_2 (12 ml) was added $Cu(OTf)_2$ (40 mg, 0.11 mmol). The resulting purplish red solution was stirred for 0.5 h at RT. Aq. $NaHCO_3$ (10 ml) was added to the reaction mixture, extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:49) as eluent furnished the dimer **25a,b** (290 mg, 62%) as white crystalline solid;

Rf = 0.35 (EtOAc-hexane 1:49); **IR** (neat): v_{max}/cm^{-1} 2928, 1471, 1453, 1377, 1253, 1173, 1090, 835, 741, 578; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 8.15 (d, *J* = 7.7 Hz, 1H), 7.63-7.58 (m, 1H), 7.44-7.18 (m, 7H), 7.11-6.93 (m, 4H), 5.32 (d, *J* = 9.3 Hz, 2H), 4.38 (dd, 9.1, 17.2 Hz, 1H), 3.81-3.64 (m, 4H), 2.97-2.78 (m, 5H), 2.30 (dt, *J* = 3.15, 9.5 and 12.5 Hz, 1H), 2.00 (s, 3H), 1.82-1.80 (m, 6H), 1.59 (s, 2H), 0.86 (s, 9H), 0.74 (s, 9H), 0.00 (s, 6H), -0.25 (s, 6H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 143.7, 138.6, 138.3, 136.0, 134.4, 133.8, 133.3, 131.5, 130.9, 128.9, 126.4, 124.8, 124.7, 123.4, 120.3, 119.4, 119.2, 118.8, 118.7, 118.3, 114.7, 110.2, 103.0, 64.1, 63.7, 62.7, 51.2, 34.9, 28.5, 27.7, 26.0, 25.8, 25.5, 18.4, 18.1, -5.2, -5.6; **HRMS**: m/z calcd for $C_{48}H_{66}N_2O_4Ssi_2Na$ [$M+Na^+$]: 823.4360; found: 823.4359.

Example 37: Synthesis of compound 26a and 26b

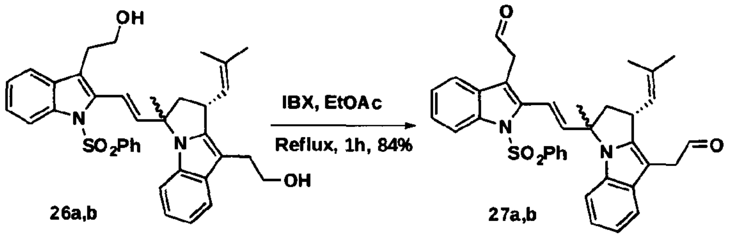


To a solution of the alcohol **18** (100 mg, 0.27 mmol) and diene **19** (134 mg, 0.27 mmol) in anhydrous CH_2Cl_2 (10 ml) was added $BF_3.OEt_2$ (150 mg, 1.05 mmol). The resulting purplish red solution was stirred for 0.5 h at RT. Aq. $NaHCO_3$ (10 ml) was added to the reaction mixture, extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (2:3) as eluent furnished the diol **26a,b** (130 mg, 78%) as yellow crystalline solid; small portion of diols **26a,b** (20mg) was purified by preparative TLC for data collection.

Rf = 0.35 (EtOAc-hexane 1:1); **IR** (neat): v_{max}/cm^{-1} 3401 (OH), 2929, 1613, 1454, 1367, 1172, 1043, 751, 586; **^{1}H NMR** ($CDCl_3$, 500 MHz) **for 26b (major isomer)**: δ 8.15 (d, *J* =

8.2 Hz, 1H), 7.65-7.03 (m, 12H), 6.21 (d, *J* = 16.2 Hz, 1H), 6.13 (d, *J* = 15.9 Hz, 1H), 5.29 (d, *J* = 9.8 Hz, 1H), 4.39 (q, *J* = 17.1 Hz, 1H), 3.81 (t, *J* = 6.1 Hz, 2H), 3.71-3.63 (m, 2H), 3.00- 2.91 (m, 2H), 2.85-2.83 (m, 1H), 2.80 (t, *J* = 6.7 Hz, 2H), 2.39-2.29 (m, 1H), 2.05 (s, 3H), 1.82 (d, *J* = 4 Hz, 6H); ^{13}**C NMR** ($CDCl_3$, 125 MHz): δ 144.3, 138.8, 137.9, 136.2, 134.8, 134.1, 133.5, 133.3, 131.8, 130.7, 128.9, 126.3, 125.1, 124.4, 123.8, 120.5, 119.1, 119.0, 118.8, 118.1, 115.1, 110.2, 103.0, 64.0, 63.1, 62.0, 50.8, 34.9, 28.2, 27.2, 25.7, 25.4, 18.1; **HRMS**: m/z calcd for $C_{36}H_{38}N_2O_4S$ [M+H$^+$]: 595.2631; found: 595.2621.

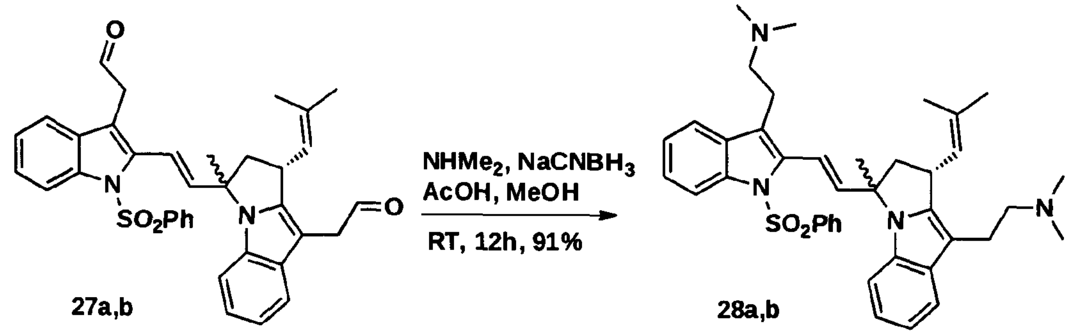
Example 38: Synthesis of compound 27a and 27b



To a solution of the alcohol **26a,b** (90 mg, 0.15 mmol) in ethyl acetate (10 ml) was added IBX (254 mg, 0.90 mmol) and refluxed for 1 h. Aq. $NaHCO_3$ was added to the reaction mixture and extracted with ethyl acetate (3 x 10 ml). The organic extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc-hexane (1:4) as eluent furnished the dial **27a,b** (75 mg, 84%) as a waxy solid;

Rf = 0.6 (EtOAc-hexane 1:4); **IR** (neat): ν_{max}/cm^{-1} 2928, 2851, 1726 (C=O), 1452, 1382, 1175, 785, 685,591; ^{1}**H NMR** (CD_3CN, 500 MHz): δ 9.6 (s, 2H), 8.1 (d, *J* = 8.5 Hz, 1H), 7.56-6.98 (m, 12H), 6.07 (d, *J* = 16.2 Hz, 1H), 5.99 (d, *J* = 16.2 Hz, 1H), 5.26 (d, *J* = 9.5 Hz, 1H), 4.40 (q, *J* = 17.4 Hz, 1H), 3.78 (d, *J* = 4.2 Hz, 2H), 3.68 (d, *J* = 2.1 Hz, 2H), 2.87 (dd, *J* = 12.5, 7.6 Hz, 1H), 2.36 (dd, *J* = 12.8, 10.1 Hz, 1H), 2.01 (s, 3H), 1.77 (d, *J* = 6.1 Hz, 6H); ^{13}**C NMR** (CD_3CN, 100MHz): δ 200.9, 200.1, 146.7, 141.0, 138.8, 137.1, 137.0, 135.9, 135.5, 134.5, 133.1, 132.0, 130.7, 127.7, 127.6, 126.8, 125.4, 125.1, 122.1, 120.8, 120.5, 119.7, 116.0, 115.5, 111.9, 98.1, 65.8, 51.7, 41.0, 39.6, 36.14, 26.13, 25.9, 18.7; **HRMS**: m/z calcd for $C_{36}H_{34}N_2O_4SNa$ [M+Na$^+$]: 591.2318; found: 591.2304.

Example 39: Synthesis of compound 28a and 28b

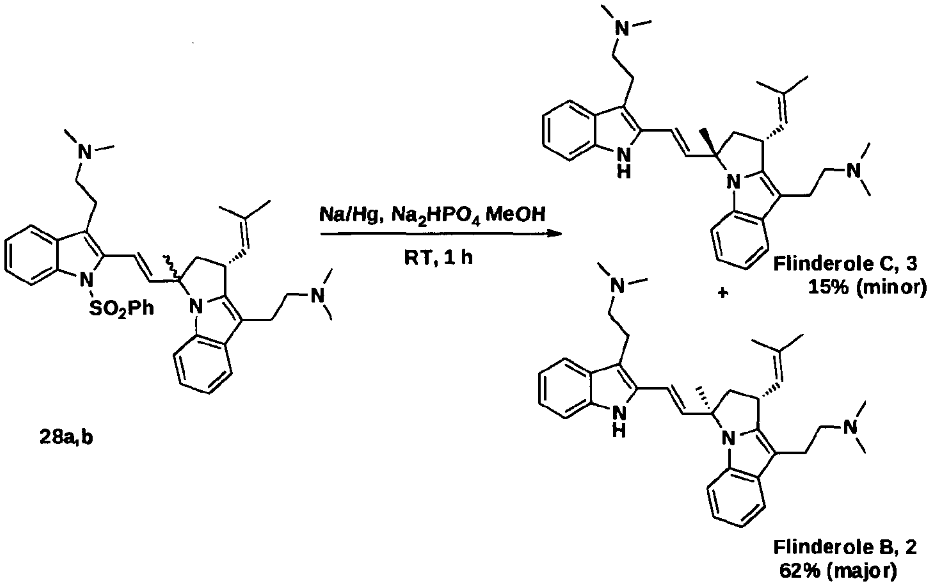


To a

mixture of $NHMe_2$ (0.30 ml, 2.0 *M* soln, 0.60 mmol) and $NaCNBH_3$ (18.5 mg, 0.30 mmol) in MeOH (2 ml) and acetic acid (0.01 ml) was added a solution of the dialdehyde **27a,b** (45 mg, 0.075 mmol) in MeOH (2 ml) and stirred for 12 h at RT. The reaction was quenched with a saturated solution of $NaHCO_3$ and extracted with ethyl acetate (2 x 5 ml), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using MeOH-CH_2Cl_2 (1:9) as eluent furnished the compound **28a,b** (45 mg, 91%) as white crystalline solid;

Rf = 0.4 (MeOH-CH_2Cl_2 1:9). **IR** (neat): v_{max}/cm^{-1} 2935, 1642, 1455, 1383, 1088, 751, 589; **^1H NMR** (CD_3OD, 400 MHz): δ 8.11 (d, *J* = 8 Hz, 1H), 7.64-6.87 (m, 12H), 6.15 (d, *J* = 16.1 Hz, 1H), 6.05 (d, *J* = 16.1 Hz, 1H), 5.35 (d, *J* = 9.8 Hz, 1H), 4.54 (m, 1H), 3.36-3.32 (m, 2H), 2.96-2.45 (m, 8H), 2.34 (s, 6H), 2.25 (s, 6H), 2.05 (s, 3H), 1.86 (d, *J* = 9.5 Hz, 6H); **^{13}C NMR** (CD_3OD, 100 MHz): δ 144.8, 139.7, 139.1, 137.7, 135.3, 135.1, 134.9, 134.4, 133.2, 132.1, 130.2, 127.5, 126.3, 126.1, 125.2, 121.7, 121.4, 120.3, 120.0, 119.6, 119.5, 116.2, 111.5, 104.8, 65.4, 61.6, 60.0, 51.6, 45.3, 45.2, 36.3, 26.1, 26.0, 23.5, 22.2, 18.6; **HRMS**: m/z calcd for $C_{40}H_{48}N_4O_2S$ $[M+H^+]$: 649.3576; found: 649.3591.

Example 40: Synthesis of flinderole B (2, Major) and flinderole C (3, Minor)



The mixture of the compound **28a,b** (180 mg, 0.36 mmol) in anhydrous MeOH (20 ml), Na_2HPO_4 (200 mg, 1.6 mmol) and Na-Hg (368 mg, 1.6 mmol) was stirred for 1 h at RT. Water (20 ml) was added to the reaction mixture, extracted with ether (3 x 15 ml), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using MeOH-CH_2Cl_2 (1:19) as eluent furnished the **flinderole C (3, Minor isomer)** (20 mg, 15 %) as a colourless waxy solid.

^{1}**H NMR** (DMSO-d$_6$, 500 MHz): δ 11.01 (s, 1H), 7.45 (dd *J* = 9.8 and 6.4 Hz, 2H), 7.24 (dd, *J* = 8.8 and 9.4 Hz, 2H), 7.06 (dd, *J* = 7.6 and 7.3 Hz, 1H), 6.94 (m, 3H), 6.61 (d, *J* = 16.2 Hz, 1H), 6.56 (d, *J* = 16.2 Hz, 1H), 5.26 (br.d, *J* = 9.8, 1H), 4.33 (ddd, *J* = 9.5, 7.9 and 7.9 Hz, 1H), 2.84-2.68 (m, 5H), 2.37-2.28 (m, 4H), 2.21 (s, 6H), 2.15 (s, 6H), 1.83 (s, 3H), 1.74 (s, 3H), 1.73 (s, 3H); ^{13}**C NMR** (DMSO-d$_6$, 125MHz): δ 142.7, 136.6, 132.8, 132.5, 132.1, 131.9, 131.0, 128.2, 125.7, 122.3, 119.9, 118.7, 118.6, 118.4, 118.4, 117.9, 113.2, 110.9, 110.0, 103.7, 63.0, 60.7, 51.2, 45.2, 45.1, 40.3, 34.9, 25.7, 23.3, 21.8, 21.7, 18.2; **HRMS**: m/z calcd for $C_{34}H_{44}N_4$ [M+H$^+$]: 509.3644; found: 509.3656.

Flinderole C (10 mg) was treated with 0.5*M* solution of TFA in acetonitrile to obtain the TFA salt of flinderole C;

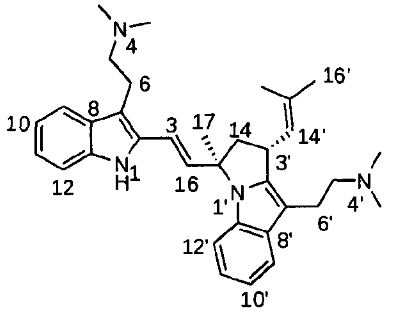
IR (neat): v_{max}/cm^{-1} 3434, 2990, 2254, 2128, 1660, 1026, 825,762; ^{1}**H NMR** (DMSO-d$_6$, 500 MHz): δ 11.23 (s, 1H), 10.22 (brs, 2H, TFA protons), 7.60 (d, *J* = 7.8 Hz, 1H), 7.58-7.56 (m, 1H), 7.36-7.29 (m, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.11 (dd, *J* = 7.8 and 7.8 Hz, 1H), 7.02-6.99 (m, 3H), 6.86 (d, *J* = 16.2 Hz, 1H), 6.66 (d, *J* = 16.2 Hz, 1H), 5.28 (br.d, *J* = 9.6 Hz, 1H), 4.40 (ddd, *J* = 9.6, 9.0 and 7.8 Hz, 1H), 3.29-2.19 (m, 5H), 3.11-3.05 (m, 1H), 2.96 (m, 2H), 2.87 (s, 6H), 2.86 (s, 6H), 2.73 (dd, *J* = 12.6, 7.8 Hz, 1H), 2.33 (dd, *J* = 12.6, 9.0 Hz, 1H), 1.86 (s, 3H), 1.80 (s, 3H), 1.74 (s, 3H); ^{13}**C NMR** (DMSO-d$_6$, 125MHz): δ 142.9, 136.3, 133.3, 133.1, 132.2, 131.8, 130.6, 127.3, 124.3, 122.4, 120.1, 118.7, 118.4, 118.3, 118.1, 117.5, 110.7, 109.7, 108.9, 99.6, 62.7, 56.8, 56.6, 50.6, 42.1, 41.9, 41.8, 41.6, 34.5, 25.2, 22.2, 18.8, 18.4, 17.8.

Further elution of the column with MeOH-CH_2Cl_2 (1:9) gave the **flinderole B (2, Major isomer)** (89 mg, 62 %) as a white waxy solid.

^{1}**H NMR** (DMSO-d$_6$, 500 MHz): δ 10.9 (s, 1H), 7.48 (dd, *J* = 8.5 and 7.0 Hz, 1H), 7.39 (dd, *J* = 7.8 and 5.2 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.07-6.97 (m, 3H), 6.93-6.90 (m, 1H), 6.47 (d, *J* = 16.0 Hz, 1H), 5.87 (d, *J* = 16.0 Hz, 1H), 5.30 (br.d, *J* = 9.6 Hz, 1H), 4.16 (dd, *J* = 8.8 and 8.4 Hz, 1H), 2.79-2.73 (m, 3H), 2.61-2.45 (m, 4H), 2.42-2.36 (m, 1H), 2.32-2.37 (m, 1H), 2.23 (s, 6H), 2.20-2.09 (m, 2H), 2.03 (s, 6H), 1.95 (s, 3H), 1.79 (s, 6H); ^{13}**C NMR** (DMSO-d$_6$, 125MHz): δ 142.9, 136.6, 132.7, 132.6, 131.8, 131.4, 131.1, 128.1, 125.2, 122.2, 120.2, 118.7, 118.5, 118.5, 118.4, 116.4, 112.7, 110.9, 110.3, 103.8, 63.8, 60.7, 60.4, 51.0, 45.1, 44.9, 34.5, 25.7, 25.5, 21.6, 21.5, 18.2; HRMS: m/z calcd for $C_{34}H_{44}N_4$ [M+H$^+$]: 509.3644; found: 509.3656.

Flinderole B (30 mg) was treated with 0.5*M* solution of TFA in acetonitrile to obtain the TFA salt of flinderole B;

IR (neat): v_{max}/cm^{-1} 3229 (NH), 2931, 1613, 1455, 1345, 1040, 745, 661, 592; ^{1}**H NMR** (DMSO-d$_6$, 500 MHz): δ 11.19 (s, 1H), 10.37 (s, 1H, TFA proton), 10.26 (s, 1H, TFA proton), 7.60 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.09 (dd, *J* = 7.8 and 7.8 Hz, 1H), 7.05 (dd, *J* = 7.8 and 7.8 Hz, 1H), 7.03 (dd, *J* = 7.8 and 7.8 Hz, 1H), 6.97 (dd, 7.8 and 7.8 Hz, 1H), 6.54 (d, *J* = 16.2 Hz, 1H), 6.34 (d, *J* = 16.2 Hz, 1H), 5.32 (br.d, *J* = 9.0 Hz, 1H), 4.28 (ddd, *J* = 9.0, 8.4 and 8.0 Hz, 1H), 3.29-3.22 (m, 1H), 3.13-3.04 (m, 3H), 3.01-2.88 (m, 6H), 2.86 (s, 6H), 2.75 (s, 6H), 2.32 (dd, *J* = 12.6 and 8.4 Hz, 1H), 1.96 (s, 3H), 1.83 (s, 3H), 1.80 (s, 3H); ^{13}**C NMR** (DMSO-d$_6$, 125MHz): δ 143.5, 136.3, 133.2, 132.2, 132.0, 131.9, 130.9, 127.4, 124.5, 122.3, 120.3, 118.7, 118.5, 118.2, 118.2, 116.0, 110.7, 110.1, 108.5, 99.8, 63.4, 56.9, 56.6, 50.5, 42.1, 42.0, 41.7, 41.5, 34.3, 25.2, 24.7, 18.6, 18.5, 17.8.

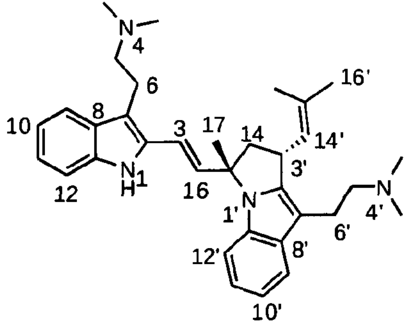


Flinderole B (**2**)

Comparative table of the spectral characteristics of Synthetic Flinderole (B) and Natural Flinderole (B)

	Natural flinderole B (**2**)	Synthetic flinderole B (**2**)	Natural flinderole B (**2**)	Synthetic flinderole B (**2**)
Position	δC (150 MHz) **(Chemical shifts determined from 2D experiments)**	δC (125 MHz)	δH (600 MHz) (mult, J Hz)	δH (500 MHz) (mult, J Hz)
1 (N)			11.12 (s)	11.19 (s)
2	132.1	132.0		
3	115.9	116.0	6.35 (d, 16.2)	6.34 (d, 16.2)
4 (N)			8.75 (m)/8.47 (m)	10.37 (br s)/10.26 (br s)
N4-Me_2	41.8	41.7, 41.5	2.75 (s, 6H)	2.75 (s, 6H)
5	56.4	56.6	3.12 (m)	3.12 (m)
			2.98 (m)	2.98 (m)
6	18.5	18.6	2.98 (m, 2H)	2.98 (m, 2H)
7	108.8	108.5		
8	127.4	127.4		
9	118.0	118.2	7.54 (d, 7.8)	7.54 (d, 7.8)
10	118.5	118.5	6.98 (dd, 7.8, 7.8)	6.97 (dd, 7.8, 7.8)
11	122.0	122.3	7.09 (dd, 7.8, 7.8)	7.09 (dd, 7.8, 7.8)
12	110.6	110.7	7.25 (d, 7.8)	7.25 (d, 7.8)
13	136.2	136.3		
14	50.5	50.5	2.88 (dd, 12.6, 8.0)	2.88 (dd, 12.6, 8.0)
			2.32 (dd,	2.32 (dd,

			12.6, 8.4)	12.6, 8.4)
15	63.7	63.4		
16	132.2	132.2	6.52 (d, 16.2)	6.54 (d, 16.2)
17	24.7	24.7	1.95 (s)	1.96 (s)
2'	143.5	143.5		
3'	34.1	34.3	4.27 (ddd, 9.0, 8.4, 8.0)	4.28 (ddd, 9.0, 8.4, 8.0)
4' (N)			8.75 (m)/8.47 (m)	10.37 (br s) / 10.26 (br s)
N4'-Me$_2$	41.8	42.0, 42.1	2.85 (s, 6H)	2.86 (s, 6H)
5'	56.7	56.9	3.07 (m)	3.07 (m)
			3.24 (m)	3.25 (m)
6'	18.5	18.5	2.98 (m, 2H)	2.98 (m, 2H)
7'	99.9	99.8		
8'	131.8	131.9		
9'	118.0	118.2	7.58 (d, 7.8)	7.60 (d, 7.8)
10'	118.4	118.4	7.03 (dd, 7.8, 7.8)	7.03 (dd, 7.8, 7.8)
11'	120.1	120.3	7.05 (dd, 7.8, 7.8)	7.05 (dd, 7.8, 7.8)
12'	109.9	110.1	7.43 (d, 7.8)	7.44 (d, 7.8)
13'	130.9	130.9		
14'	124.4	124.5	5.32 (br d, 9.0)	5.32 (br d, 9.0)
15'	133.3	133.2		
16'	17.8	17.8	1.83 (s)	1.83 (s)
17'	25.1	25.2	1.80 (s)	1.80 (s)



Flinderole C (**3**)

Comparative table of the spectral characteristics of Synthetic Flinderole (C) and Natural Flinderole (C)

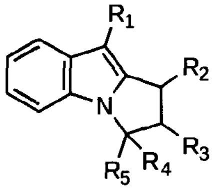
	Natural flinderole C (**3**)	Synthetic flinderole C (**3**)	Natural flinderole C (**3**)	Synthetic flinderole C (**3**)

	(Chemical shifts determined from 2D experiments)			
Position	δC (150 MHz)	δC (125 MHz)	δH (mult, J Hz)(600 MHz)	δH (mult, J Hz)(500 MHz)
1 (N)			11.19 (s)	11.23 (s)
2	132.3	132.2		
3	117.4	117.5	6.85 (d, 16.2)	6.86 (d, 16.2)
4 (N)				10.21 (br s)
N4-Me_2	41.9	42.1, 41.9	2.86 (s, 6H)	2.86 (s, 6H)
5	56.8	56.8	3.17 (m, 2H)	3.17 (m, 2H)
6	18.9	18.8	3.17 (m, 2H)	3.17 (m, 2H)
7	109.1	108.9		
8	127.4	127.3		
9	118.1	118.1	7.60 (d, 7.8)	7.60 (d, 7.8)
10	118.5	118.4	7.01 (dd, 7.8, 7.8)	7.01 (dd, 7.8, 7.8)
11	122.2	122.4	7.10 (dd, 7.8, 7.8)	7.10 (dd, 7.8, 7.8)
12	110.6	110.7	7.26 (d, 7.8)	7.26 (d, 7.8)
13	136.3	136.3		
14	50.5	50.6	2.73 (dd, 12.6, 7.8)	2.73 (dd, 12.6, 7.8)
			2.33 (dd, 12.6, 9.0)	2.33 (dd, 12.6, 9.0)
15	62.9	62.7		
16	132.9	133.1	6.66 (d, 16.2)	6.66 (d, 16.2)
17	22.2	22.2	1.74 (s)	1.74 (s)
2′	143.1	142.9		
3′	34.5	34.5	4.40 (ddd, 9.6, 9.0, 7.8)	4.40 (ddd, 9.6, 9.0, 7.8)
4′ (N)				10.21 (br s)
N4′-Me_2	41.9	41.6, 41.8	2.85 (s, 6H)	2.86 (s, 6H)
5′	57.0	56.8	3.22 (m)	3.22 (m)
			3.08 (m)	3.08 (m)
6′	18.4	18.4	2.95 (m, 2H)	2.95 (m, 2H)
7′	99.7	99.6		
8′	131.5	131.8		
9′	118.0	118.1	7.56 (m)	7.58-7.56 (m)
10′	118.5	118.7	7.00 (m)	7.02-6.99

				(m)
11'	119.5	120.1	7.00 (m)	7.02-6.99 (m)
12'	109.6	109.7	7.29 (m)	7.36-7.29 (m)
13'	131.0	130.6		
14'	124.2	124.3	5.28 (br d, 9.6)	5.28 (br d, 9.6)
15'	133.4	133.3		
16'	17.8	17.8	1.86 (s)	1.86 (s)
17'	25.2	25.2	1.80 (s)	1.80 (s)

We claim

1. Compounds of general formula I



General Formula I

wherein,

R_1 is selected independently from $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$.

R_2 is selected independently from$-CH=CH_2$, -CH=CHMe, $-CH=CMe_2$, -CH=CHEt, $-CH=CEt_2$, -CH=CH(Pr), $-CH=C(Pr)_2$, -CH=CH(i-Pr), $-CH=C(i-Pr)_2$, -CH=CHPh, $-CH=C(Ph)_2$, -Ph, -PhCl, $-PhCH_3$, -PhOMe, $-CH_2Ph$, $-CH_2PhCH_3$, $-CH_2PhOMe$, $-CH(Me)_2$, $-CH_2CH_3$, $-C(Me)_3$, $-C_6H_6$, $-CH_2CH=CH_2$, -CHMeEt, $-CH_2C(Me)_3$, $-CH_2CH=CH_2$, -CCPh.

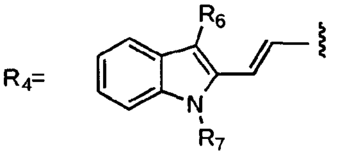
R_3 is selected independently from -H, CH3, -Ph, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, - $CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$,

-COCONHMe, -$COCONMe_2$, -$CH_2CH_2CO_2H$, -$CONHNH_2$, -$CH_2CONHNH_2$, -$COCONMe_2$, -SH, -SC_2H_5, -$SCH=CH_2$, -$CH_2CH_2CH_2CO_2H$, -$OCOCH_3$, -$OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, -$CH_2CO_2CH_3$, -$CH_2CO_2CH_2CH_3$, -COCH2Ph, -$COCH_2Ph$, -COCOCl, -$OCO(CH_2)_6Me$.

R_4 is selected independently from -H, CH3, -Ph, -CH_2CH_3, -$CH_2CH_2CH_3$, -Br, -Cl, -F, -I, -CH_2OH, -CH_2OCH_3, -CH_2OBn, -$CH_2OCH_2CH_3$, -CH_2CH_2OH, -CH_2CH_2Br, -$CH_2CH_2NH_2$, -CH_2CH_2NHMe, -$CH_2CH_2NMe_2$, -CH_2NH_2, -CH_2NHMe, CH_2NMe_2, - (4-Fluorophenyl), -CO_2H, -$CH_2CH=CH_2$, -$CH=CMe_2$, -$CH=CEt_2$, -OCH_3, OCH_2CH_3, -$COCH_3$, -OH, -CHO, -$CONH_2$, -CH_2CONH_2, -$CH_2CONHMe$, -CH_2CONMe_2, -$CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, -$CH_2CH_2CONMe_2$, -CN, -CH_2CN, -CH_2CO_2H, -CH_2CO_2Me, -CH_2CO_2Et, - (2-Nitrovinyl), -$CH_2=CHCO_2H$, -$CH=CHCO_2Me$, -$CH=CHCO_2Et$, -$CH_2=CHCN$, -$COCO_2H$, -$COCONH_2$, -COCONHMe, -$COCONMe_2$, -$CH_2CH_2CO_2H$, -$CONHNH_2$, -$CH_2CONHNH_2$, -$COCONMe_2$, -SH, -SC_2H_5, -$SCH=CH_2$, -$CH_2CH_2CH_2CO_2H$, -$OCOCH_3$, -$OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, -$CH_2CO_2CH_3$, -$CH_2CO_2CH_2CH_3$, -COCH2Ph, -$COCH_2Ph$, -COCOCl, -$OCO(CH_2)_6Me$.

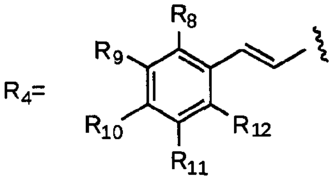
R_5 is selected independently from -CH3, -$CH=CH_2$, -CH=CHMe, -$CH=CMe_2$, -CH=CHEt, -$CH=CEt_2$, -CH=CH(Pr), -$CH=C(Pr)_2$, -CH=CH(i-Pr), -$CH=C(i\text{-}Pr)_2$, -CH=CHPh, -$CH=C(Ph)_2$, -CH=CH(Indole).

With the provisio, when R4 is as indicated herein below,



R_6 selected from -H, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -Br, -Cl, -F, -I, -CH_2OH, -CH_2OCH_3, -CH_2OBn, -$CH_2OCH_2CH_3$, -CH_2CH_2OH, -CH_2CH_2Br, -$CH_2CH_2NH_2$, -CH_2CH_2NHMe, -$CH_2CH_2NMe_2$, -CH_2NH_2, -CH_2NHMe, CH_2NMe_2, - (4-Fluorophenyl), -CO_2H, -Ph, -$CH_2CH=CH_2$, -$CH=CMe_2$, -$CH=CEt_2$, -OCH_3, OCH_2CH_3, -$COCH_3$, -OH, -CHO, -$CONH_2$, -CH_2CONH_2, -$CH_2CONHMe$, -CH_2CONMe_2, -$CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, -$CH_2CH_2CONMe_2$, -CN, -CH_2CN, -CH_2CO_2H, -CH_2CO_2Me, -CH_2CO_2Et, - (2-Nitrovinyl), -$CH_2=CHCO_2H$, -$CH=CHCO_2Me$, -$CH=CHCO_2Et$, -$CH_2=CHCN$, -$COCO_2H$, -$COCONH_2$, -COCONHMe, -$COCONMe_2$, -$CH_2CH_2CO_2H$, -$CONHNH_2$, -$CH_2CONHNH_2$, -$COCONMe_2$, -SH, -SC_2H_5, -$SCH=CH_2$, -$CH_2CH_2CH_2CO_2H$, -$OCOCH_3$, -$OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, -$CH_2CO_2CH_3$, -$CH_2CO_2CH_2CH_3$, -COCH2Ph, -$COCH_2Ph$, -COCOCl, -$OCO(CH_2)_6Me$;

R_7 repesents -H, $-CH_3$, $-COCH_3$, -SO2Ph, -(BOC), -(Ph-F), -(Bn), $-(C_5H_{10}F)$, $-(CO_2Et)$, -(MOM);
With the provisio, when



R_8 represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH{=}CH_2$, $-CH{=}CMe_2$, $-CH{=}CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2{=}CHCO_2H$, $-CH{=}CHCO_2Me$, $-CH{=}CHCO_2Et$, $-CH_2{=}CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH{=}CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$.

R_9 represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH{=}CH_2$, $-CH{=}CMe_2$, $-CH{=}CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2{=}CHCO_2H$, $-CH{=}CHCO_2Me$, $-CH{=}CHCO_2Et$, $-CH_2{=}CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH{=}CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$.

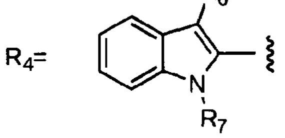
R_{10} represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH{=}CH_2$, $-CH{=}CMe_2$, $-CH{=}CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$,

$-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$.

R_{11} represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$.

R_{12} represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$.

With the provisio, when R4 is as indicated herein below,

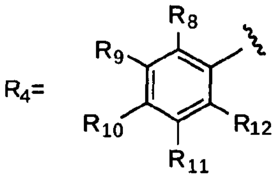


R_6 represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$,

$-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$.

R_7 = -H, $-CH_3$, $-COCH_3$, -SO2Ph, -(BOC), -(Ph-F), -(Bn), $-(C_5H_{10}F)$, $-(CO_2Et)$, -(MOM).

With the provisio, when



R_8 represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$;

R_9 represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$,

$OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$;

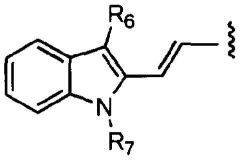
R_{10} represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$;

R_{11} represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$;

R_{12} represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -Br, -Cl, -F, -I, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OBn$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2Br$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHMe$, $-CH_2CH_2NMe_2$, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2, - (4-Fluorophenyl), $-CO_2H$, -Ph, $-CH_2CH=CH_2$, $-CH=CMe_2$, $-CH=CEt_2$, $-OCH_3$, OCH_2CH_3, $-COCH_3$, -OH, -CHO, $-CONH_2$, $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONMe_2$, $-CH_2CH_2CONH_2$, $CH_2CH_2CONHMe$, $-CH_2CH_2CONMe_2$, -CN, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, - (2-Nitrovinyl), $-CH_2=CHCO_2H$, $-CH=CHCO_2Me$, $-CH=CHCO_2Et$, $-CH_2=CHCN$, $-COCO_2H$, $-COCONH_2$, -COCONHMe, $-COCONMe_2$, $-CH_2CH_2CO_2H$, $-CONHNH_2$, $-CH_2CONHNH_2$, $-COCONMe_2$, -SH, $-SC_2H_5$, $-SCH=CH_2$, $-CH_2CH_2CH_2CO_2H$, $-OCOCH_3$, $-OCOCH_2CH_3$, $OCOCH_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -COCH2Ph, $-COCH_2Ph$, -COCOCl, $-OCO(CH_2)_6Me$;

with the provisio, when R_1 is $-CH_2CH_2NHMe$, R_2 is $-CH=CMe_{2}$., R_3 is -H, R_5 is .....CH_3,

R_4=

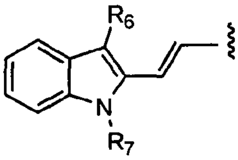


R_6 is $-CH_2CH_2NHMe$ and R_7 is -H;

with the provisio, when R_1 is $--CH_2CH_2NMe_2$, R_2 is $-CH=CMe_2$, R_3 is -H, R_5 $-CH_3$,

;

R_4=

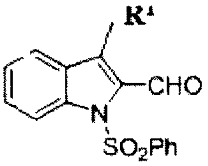


R_6 is $-CH_2CH_2NMe_2$ and R_7 is -H are excluded.

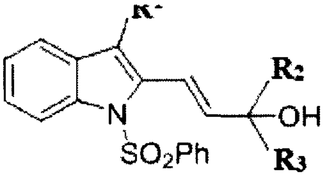
2. The compound as claimed in claim 1, wherein said compounds are useful as anti-malarial compound.

3. A process for the preparation of Flinderole A-C and compounds of general formula I as claimed in claim 1 comprising the steps of:

a. reacting indole aldehyde (1c') with Ph3P=CHCO2Et followed by reaction of the resultant ester with MeMgBr to obtain tertiary alcohol (1d');

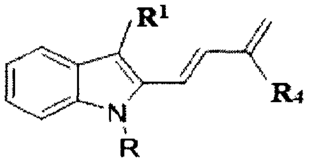


1c'



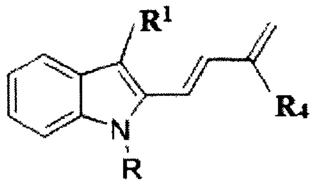
1d'

b. mesylating tertiary alcohol (1d') as obtained in step (a) followed by elimination to obtain sulphonated diene (1b');



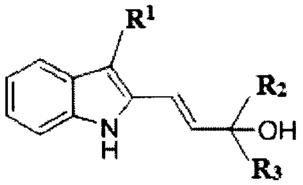
1b' R = SO_2Ph

c. desulfonylating (1b') as obtained in step (b) using methanolic NaOH to obtain desulphonated diene (1e');



1e' R = H

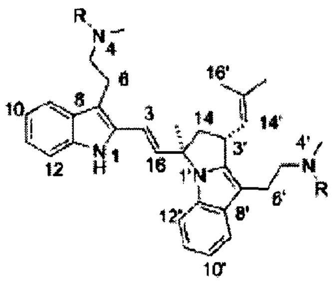
d. desulfonylating alcohol (1d') as obtained in step (a) with sodium amalgam to obtain alcohol (1a'); and

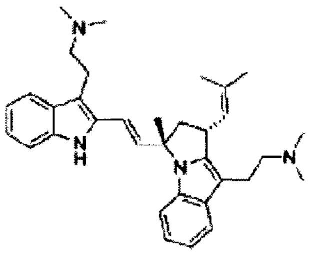


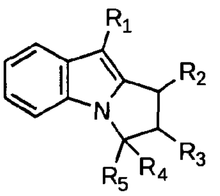
1a'

e. reacting alcohol (1a') as obtained in step (d) optionally with sulphonated diene (1b') as obtained in step (b) or desulphonated diene (1e') as obtained in step (c) in presence of Lewis acid and a non- polar solvent at temperature in the range of 25 to 32°C to obtain sulphonated or desuphonated compound of general formula 1;

f. desulfonylating sulphonated compound of general formula 1 as obtained in step (e) using methanolic NaOH to obtain desulphonated Flinderole A-C and compounds of general formula I .







Flinderole A (R=H) Flinderole C **General Formula I**
Flinderole B (R=H)

4. The process as claimed in claim 1, wherein Lewis acid used in step (e) is selected

from Cu(OTf)2 or $BF_3 \cdot OEt_2$.

5. The process for the preparation of compounds of general formula I as claimed in claim 1, optionally comprising dimerization of alcohol (1a') and the said process comprising the steps of:

a. adding alcohol (1a') with lewis acid with stirring foer period in the range of 50 to 70 minutes at temperature in the range of 25 to 32°C followed by adding water to obtain reaction mixture;

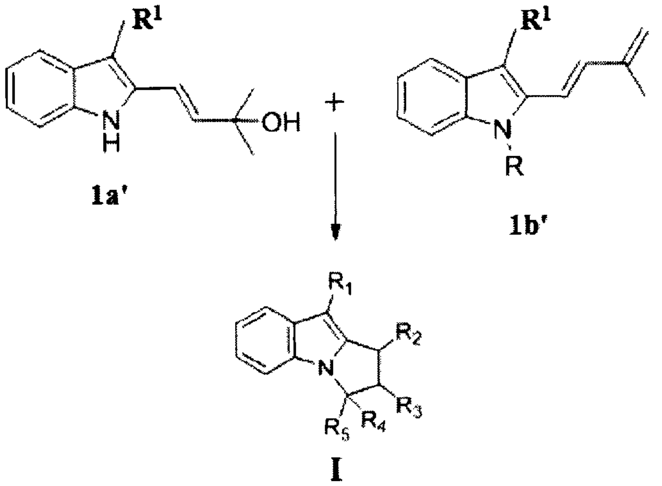
b. extracting the reaction mixture as obtained in step (a) with non-polar solvent, washing with brine, drying followed by evaporating the solvent;

c. purifying the residue on silica gel column using EtOAc-hexane (1:39) to obtain compound of general formula 1.

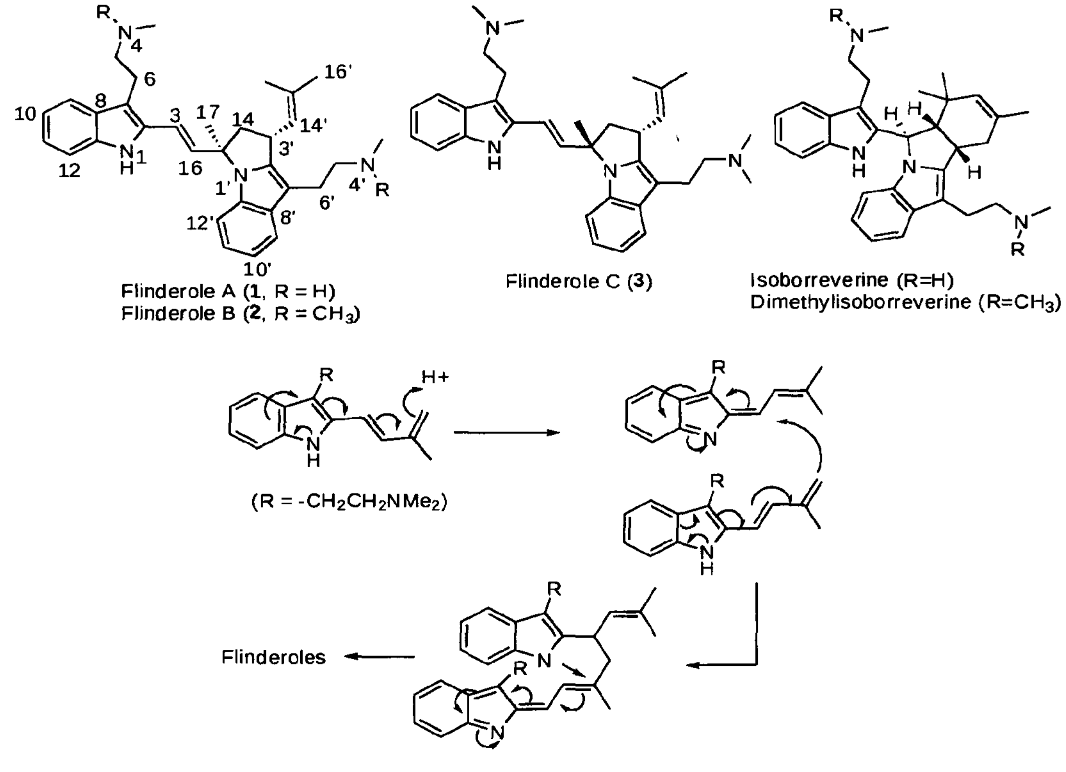
6. The process as claimed in claim 6, wherein Lewis acid used in step (a) is selected from Cu(OTf)2 or $BF_3 \cdot OEt_2$.

7. A pharmaceutical composition for the treatment of malaria comprising compounds of general formula I optionally along with pharmaceutically acceptable excipients.

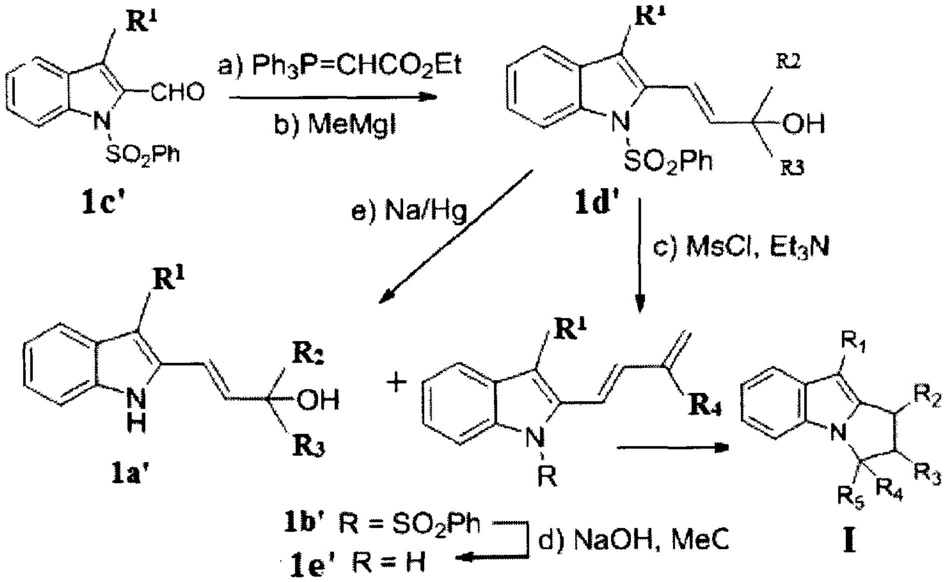
8. The compounds of general formula 1 useful as anti-malarial compound and process for the preparation thereof substantially as herein described with references of examples and drawing accompanying the specification.



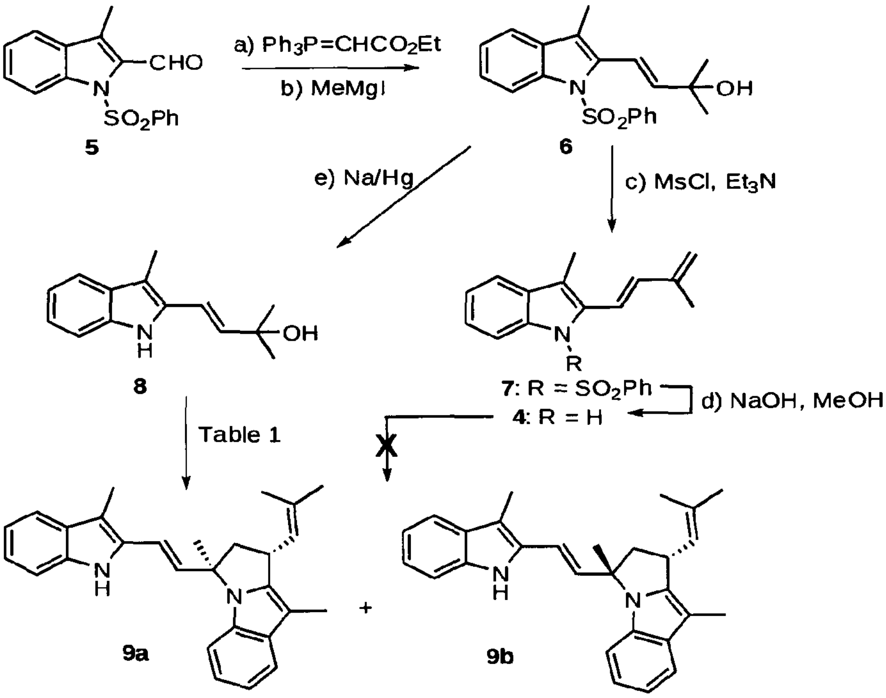
Scheme 1



Scheme 2



Scheme 3



Scheme 4

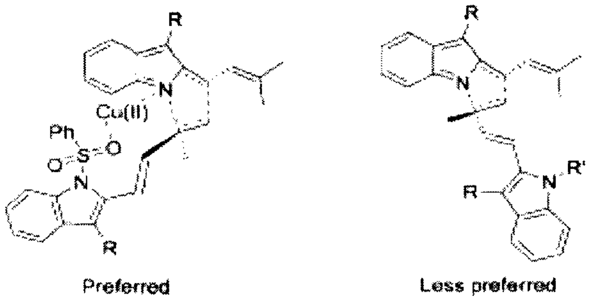
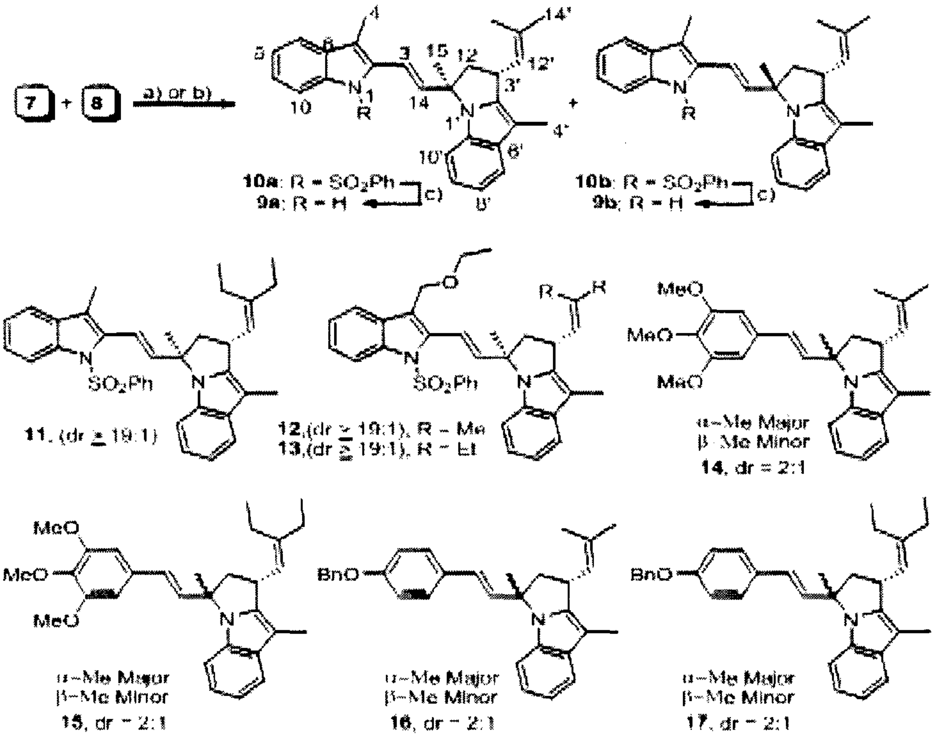
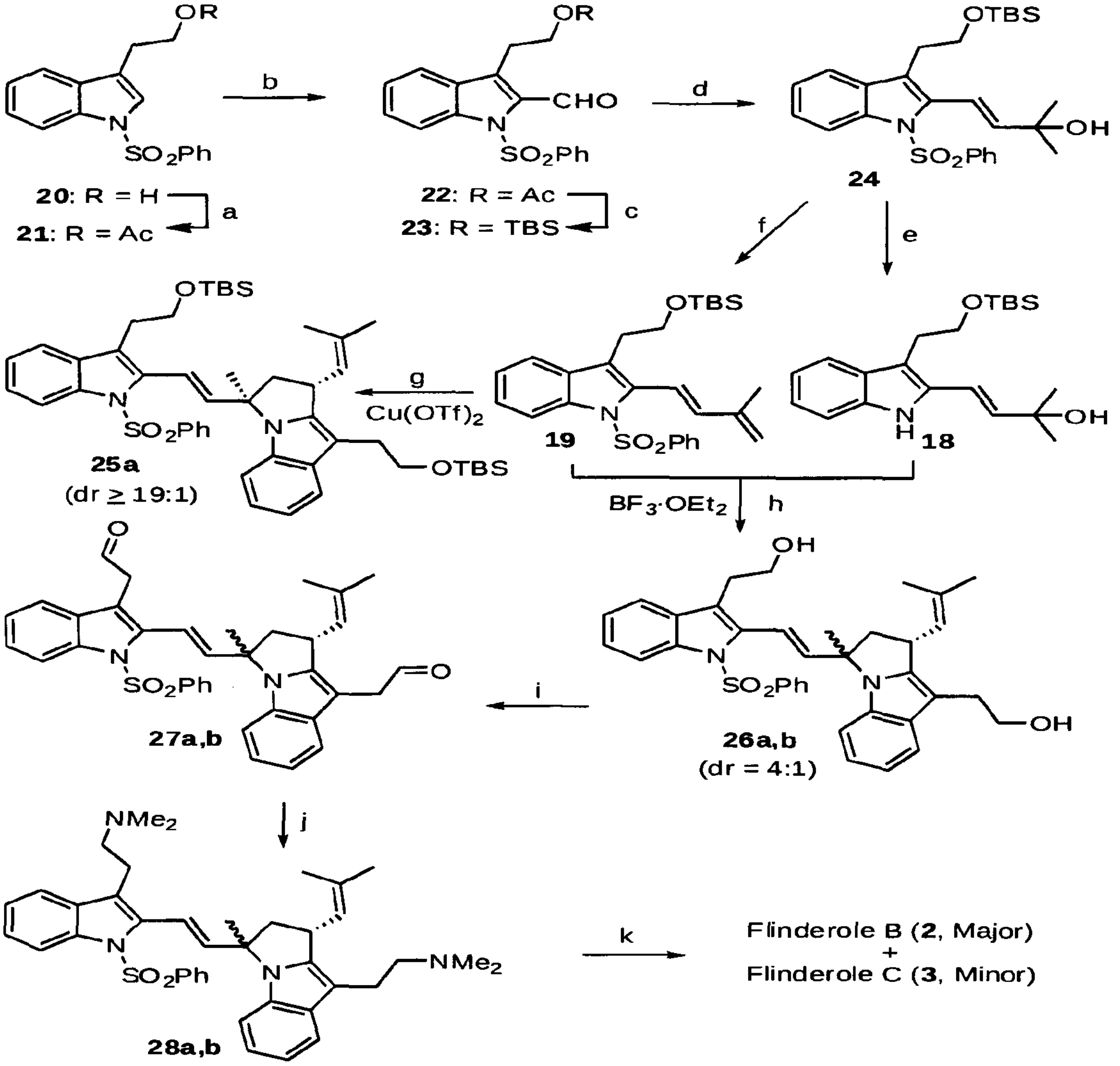


Figure 1. Proposed stereochemical model for the [3 + 2] cycloaddition.



Scheme 5

(a) Cu(OTf)$_2$ (0.2 equiv.), CH$_2$Cl$_2$, RT, 30 min., 95%; (b) BF$_3$·OEt$_2$ (0.2 equiv.), CH$_2$Cl$_2$, RT, 20 min., 92%; (c) Na/Hg (4.0 equiv), Na$_2$HPO$_4$ (4.0 equiv), MeOH, RT, 1 h, 94%.



Scheme 6

(a) Ac_2O (5.0 equiv), DMAP (0.2 equiv), Pyridine (5.0 equiv), CH_2Cl_2, RT, 6 h, 91%; (b) Dichloromethyl methyl ether (5.0 equiv), stannic chloride (5.0 equiv), CH_2Cl_2, -78 to -10 °C, 1 h, 80%; (c) i. LiOH (5.0 equiv), H_2O, THF, RT, 3 h: ii. TBSCl (1.3 equiv), imidazole (1.5 equiv), CH_2Cl_2, 0 °C to RT, 6 h, 81% (over 2 steps); (d) i. $Ph_3P{=}CHCO_2Et$ (1.5 equiv), CH_2Cl_2, RT, 6 h, 91%; ii. MeI (10 equiv), Mg turnings (9 equiv), I_2 (cat.), Et_2O, 0 °C to RT, 2 h, 89%; (e) Na/Hg (4.0 equiv), Na_2HPO_4 (4.0 equiv), MeOH, RT, 1 h, 97%; (f) MsCl (3.0 equiv), Et_3N (6.0 equiv), THF, 0 °C to reflux, 2 h, 81%. (g) $Cu(OTf)_2$ (0.2 equiv), CH_2Cl_2, RT, 30 min, 62%. (h) $BF_3{\cdot}OEt_2$ (4.0 equiv), CH_2Cl_2, RT, 30 min. 78%; (i) IBX (6.0 equiv), EtOAc, reflux, 1 h, 84%; (j) $NHMe_2$ (4.0 equiv), $NaCNBH_3$ (4.0 equiv), AcOH (cat.), MeOH, RT, 12 h, 91%; (k) Na/Hg (4.0 equiv), Na_2HPO_4 (4.0 equiv), MeOH, RT, 1 h, **2** (62%), **3** (15%).

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2011/000899

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04
ADD.

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FERNANDEZ L S ET AL: "Flinderoles A-C: Antimalarial Bis-indole Alkaloids from Flindersia Species", ORGANIC LETTERS, vol. 11, no. 2, 17 December 2008 (2008-12-17), pages 329-332, XP002671883,	1,2,7,8
A	page 331, left-hand column, line 11 - page 331, right-hand column, line 7; figure 1 ----- -/--	3-6

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

☒ See patent family annex.

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Date of the actual completion of the international search 20 March 2012	Date of mailing of the international search report 05/04/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Usuelli, Ambrogio

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FERNANDEZ L S ET AL: "Antiparasitic activity of alkaloids from plant species of Papua New Guinea and Australia", INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, vol. 36, no. 3, 1 September 2010 (2010-09-01), pages 275-279, XP027147676, ELSEVIER SCIENCE, AMSTERDAM, NL ISSN: 0924-8579 [retrieved on 2010-07-16]	1,2,7,8
A	table 1 -----	3-6
X,P	DATTATRAYA H D ET AL: "Biomimetic Total Synthesis of Flinderoles B and C", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 133, no. 9, 11 February 2011 (2011-02-11), pages 2864-2867, XP002671884, Schemes 2-4 -----	1-8
A	WO 2006/046949 A1 (WALTER REED ARMY INST OF RES W [US]; AI J LIN [US]; JIAN GUAN [US]; QU) 4 May 2006 (2006-05-04) claims 1,31 -----	1-8
A	WO 2009/153516 A1 (SANOFI AVENTIS [FR]; ALASIA MARCEL [FR]; MINOUX HERVE [FR]; RUXER JEAN) 23 December 2009 (2009-12-23) claims 1,18 -----	1-8
A	WO 2009/094157 A1 (ARENA PHARM INC [US]; JONES ROBERT M [US]; BUZARD DANIEL J [US]; KAWAS) 30 July 2009 (2009-07-30) figure 7 -----	3-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2011/000899

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006046949 A1	04-05-2006	NONE	
WO 2009153516 A1	23-12-2009	AR 072119 A1	04-08-2010
		AU 2009261785 A1	23-12-2009
		CA 2727626 A1	23-12-2009
		CN 102124008 A	13-07-2011
		CO 6280537 A2	20-05-2011
		EP 2313412 A1	27-04-2011
		FR 2932484 A1	18-12-2009
		JP 2011524410 A	01-09-2011
		KR 20110028626 A	21-03-2011
		TW 201000482 A	01-01-2010
		US 2011184015 A1	28-07-2011
		UY 31901 A	29-01-2010
		WO 2009153516 A1	23-12-2009
WO 2009094157 A1	30-07-2009	AU 2009206733 A1	30-07-2009
		CA 2711887 A1	30-07-2009
		CN 101981030 A	23-02-2011
		EP 2252615 A1	24-11-2010
		JP 2011510073 A	31-03-2011
		US 2010292233 A1	18-11-2010
		WO 2009094157 A1	30-07-2009