Iodine catalyzed mild and efficient method for the synthesis of flavones

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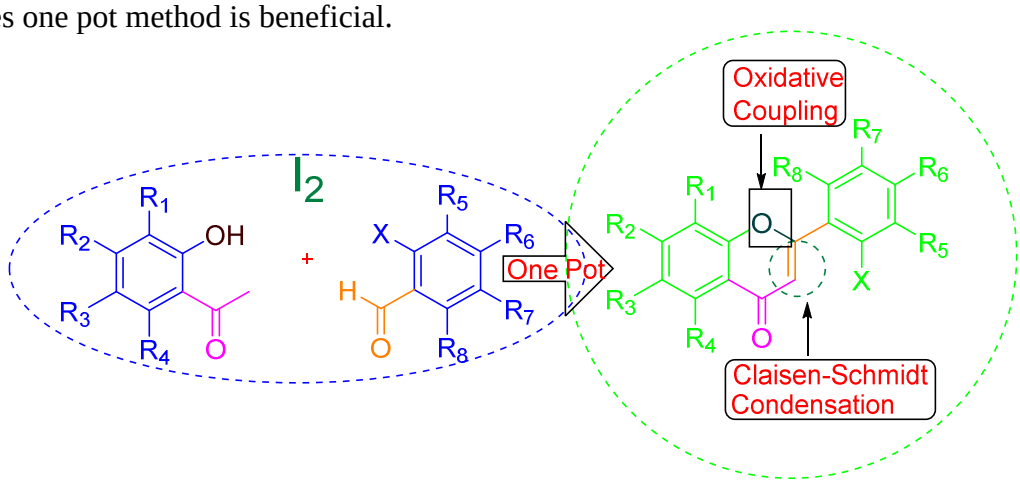
Abstract

Convenient, facile, and one pot method of medicinally important flavones is invented. Substituted 2-hydroxy acetophenone and substituted aldehydes treated in presence of iodine catalyst to give flavones. We synthesized more than 15 flavones molecules by one pot method. This new protocol minimizes the number of steps in the synthesis of flavones. This novel method invented is useful to most of pharmaceutical industries in the word. Most of anticancer, antifungal, anti-inflammatory drugs are derivatives of flavones. For these industries one pot method is beneficial.

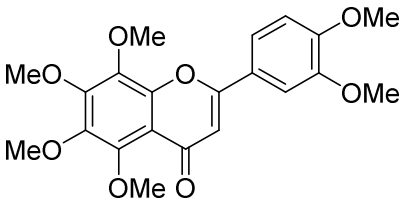


KEYWORDS: Flavones, One pot method, Iodine, Natural products.

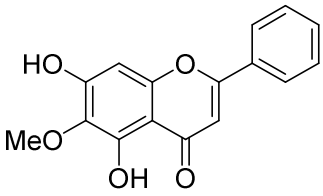
Introduction

Flavonoids are common components of human diet as they are found in foods (fruits and vegetables) and beverages (red wine, tea, and juices). Red wine contains high levels of flavonoids, mainly Quercetin and Rutin. Many studies have confirmed that one or two glasses of red wine daily can protect against heart disease i.e., the intake of red wine reduces the coronary heart disease. Flavonoids are natural products, found in plants as secondary

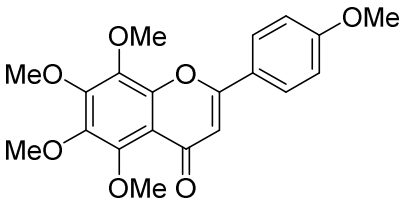
metabolite[7].Flavonoids have wide spectrum of bio- activities[13]. Increasingly, flavonoids are becoming the subject of medical research. Many drugs available today are either from plant source or modified from the plant derived compounds. Flavonoids are among the most ubiquitous polyphenolic compounds found in nature that show wide range of biological activity.viz.anticancer[8].antiviral[27],antioxidant[28],antimalarial[17],antiinflammatory[15],antifungal[26], antiallergic,anti-diabetic[16],antimicrobial[26],cardio protective agents[1] and anti-protozoan[33] etc. Some basic flavones skeletons are shown below,



Nobiletin



Oroxylin-A



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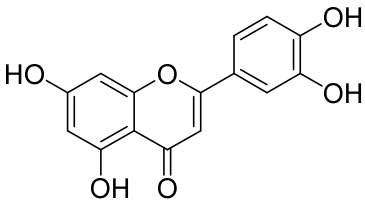
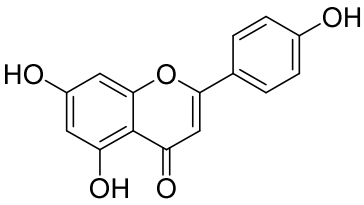
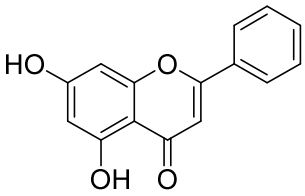


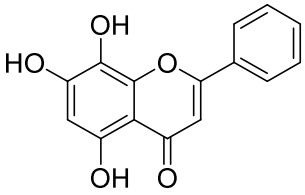
Luteolin



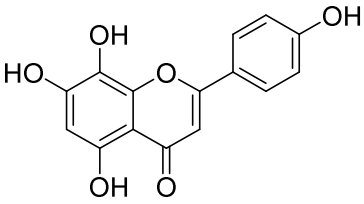
Apigenin



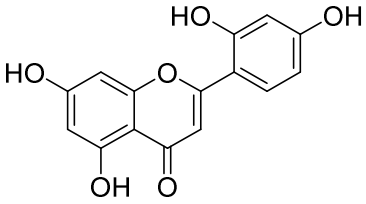
Chrysin



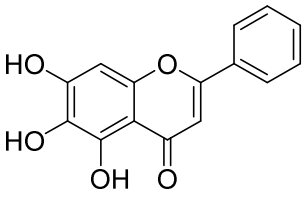
Norwogonin



Scutellarin



Noratocarpetin



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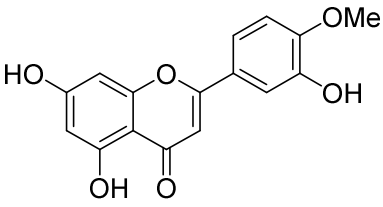
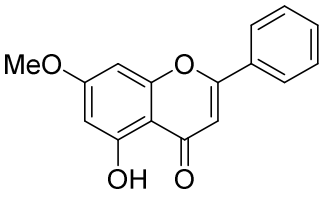
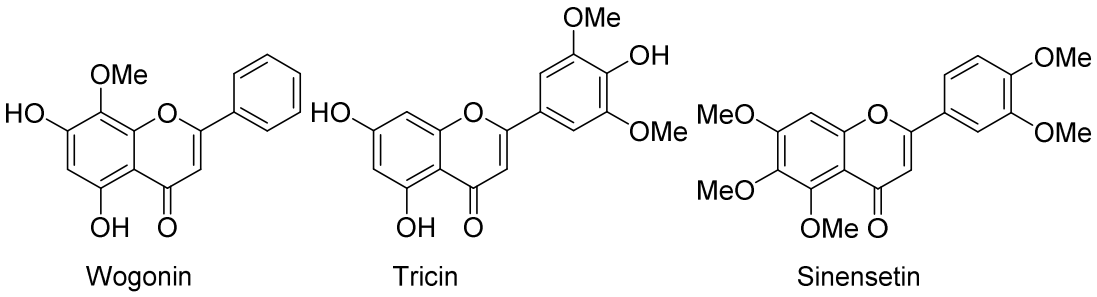


Diosmetin



Tectochrysin



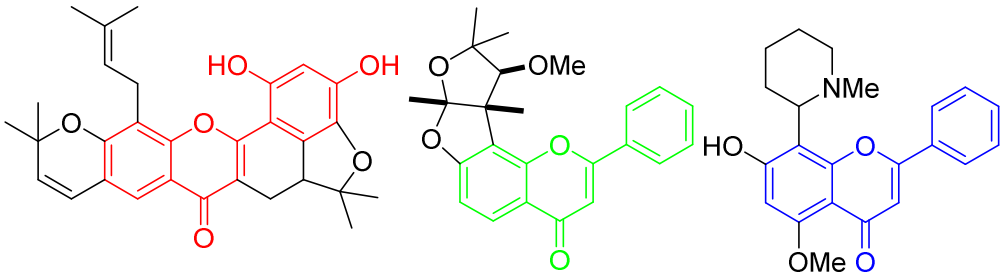


Table1.Previous Multistep synthesis of flavones (**Scheme1, 2**).

Methods	Reagent
1.Baker-Venkatraman[1,2]	Na_2CO_3 or HCl/Ethanol
2. Claisen Schmidt[9-12]	I_2/DMSO
3. Allan-Robinsons[14,18.19]	Photon/Heat
4. George W. Kabalka	$CuCl_2$,Ethanol
5. A.K.Ganguly [60]	DBU/Pyridine
6. Wesseley-Moser Reaction[23]	Acid or Base

7.Algar- Flynn-Oyamada reaction [20]	H_2O_2
8.Auwers synthesis[21,29,30]	HCl,Br_2
9.Sarda,Pathan[22]	$EtNH_2/HNO_{2(MW)}$
10. Suzuki-Miyaura reaction[25]	$Pd(PPh_3)_4/CsCO_3$
11. Von-Konstanecki method[6465]	C_5H_5ONO/H_2SO_4
12.Wittig reaction	$Et_3N,H_2O/PPh_3$[46,59]

Most of the methods for the synthesis of flavones are based on Claisen Schmidt and Baker-Venkatraman methods or modification in these methods (**Table 1**). Chalcone cyclised to flavones by oxidative coupling method or 1,3-diones undergo cyclization to flavones. Preparation of these two intermediate is time consuming and low to moderate yields. For these cyclisation in past number of reagents used (**Table 2.**)

Table2. Catalyst used for the cyclization of Chalcone & 1, 3 dione.

Cyclization of Chalcone /dione	Reagent or catalyst
1. Chalcone	AlCl3[55]
2. Chalcone	$ZnCl_2$[55]
3. Chalcone	BF3.OEt2[55]
4. Chalcone	$SnCl_2.2H_2O$[55]

5. Chalcone	$HgCl_2$[55]
6. Chalcone	$FeCl_3$[55]
7. Chalcone	$SnCl_4$[55]
8. Chalcone	Iodine(Solvent fee)[55]
9. 1,3 dione	Amberlyte-15[34]
10. 1,3 dione	$FeCl_3$[35]
11. 1,3 dione	$Br_2/CHCl_3$[36]
12. 1,3 dione	HCl/EtOH[37]
13. 1,3 dione	Clay[38]
14. 1,3 dione	AcONa/AcOH[39]
15. 1,3 dione	H_2SO_4[40]
16. 1,3 dione	Co III (Sulphur)OH[41]
17. Chalcone	I_2/DMSO[42]
18. Chalcone	SeO_2/DMSO[43]
19. Chalcone	DDQ / Dioxane[44]
20. Chalcone	Br2/NaOH[45]
21. Chalcone	SeO2/pentanol[52-54]
22. Chalcone	I_2/ Triethylene Glycol[49]
23. Chalcone	Dowex-H+,Isopropanol[47]
24. Chalcone	SeO2/Isoamyl alcohol[48]

25. 1,3 dione	$Tl(NO_2)_3.3H2O$[50]
26. Chalcone	Oxalic acid[57]
27. Chalcone	NH_4I
28. Chalcone	Nickel peroxide/Dioxane[51]
29. Chalcone	Silica gel[56]
30. Chalcone	$CuCl_2$[57]
31. Chalcone	Silica Gel /$InBr_3$[61]
32. 2-hydroxy acetophenone	K_2CO_3/wet Acetone[61]
33. Chalcone	$V_2O_3/H_2O_2/NH_4Br$[62]
34. Direct flavones (Our Novel One Pot)	**I_2/Dioxane**

In previous methods different solvents like ethanol, methanol.DMF, DMSO, $CHCl_3$, acetonitrile & 1, 4- dioxane are used for the synthesis. Out of which we selected dioxane as a suitable solvent. It is compulsory to prepare intermediate (Chalcone & 1, 3 di-one, exceptionally one pot methods) (**Scheme-1**.) followed by cyclization in the previous method. We accepted this challenge and decided to synthesize flavones by one pot method. We selected iodine as a catalyst because of it is less toxic and easily available reagent (**Scheme-3&4**). All starting material was purchased from Sigma, Aldrich & Merck chemicals. Carefully studying all previous methods and catalysts we selected dioxane as solvent for synthesis. All reactions were initially monitored by TLC.

Experimental

All material purchased from Sigma-Aldrich & Merck chemicals from dealer at Vapi, Gujrat.

General procedure for the preparation of compound 1-15 (Table 3).

Appropriate substituted 2-hydroxy acetophenone (1mmole), substituted benzaldehyde (1 mmole) & 50 mol% Iodine is added in round bottom flask. Add dioxane as a solvent sufficient to dissolve the reactant. Stirr reaction mass for 50 minutes at 50^0C.Check TLC after 50 minutes. This indicates chalcone is formed. Same reaction mass is heated at 100-105^0C for 2 hrs. After 2 hrs, TLC shows reaction is complete. Cool to RT and add saturated sodium thiosuphate solution so that excess iodine consumed. Separate two layers and extract compound in $CHCl_3$.If necessary wash $CHCl_3$ layer by $NaHCO_3$ solution. Then pass chloroform layer through sodium sulphate so that moisture gets absorbed. Concentrate chloroform layer solid obtained. Material sent for analysis.

Results & discussion

Synthesis of flavones is a time consuming process (**Scheme1&2**).Cost of material is very high due to multistep synthesis. But for the first time we are successful to synthesize flavones in a short span of time. We synthesized flavones by novel one pot method. Iodine is a versatile reagent in most of reaction. After careful study of this catalyst we decided that iodine can be used as a catalyst for the one pot synthesis of flavones. We synthesized 12-15 flavones molecules with sufficient yield (**Table-3**).

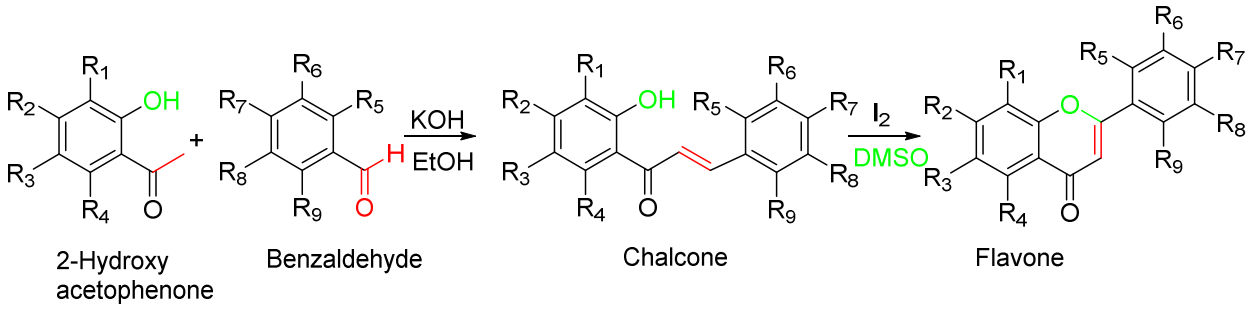
Conclusion

In conclusion, we have developed simple and efficient one pot method for the synthesis of flavones using iodine as a catalyst. In this process Claisen-Schmidt & oxidative coupling are carried out by one pot.

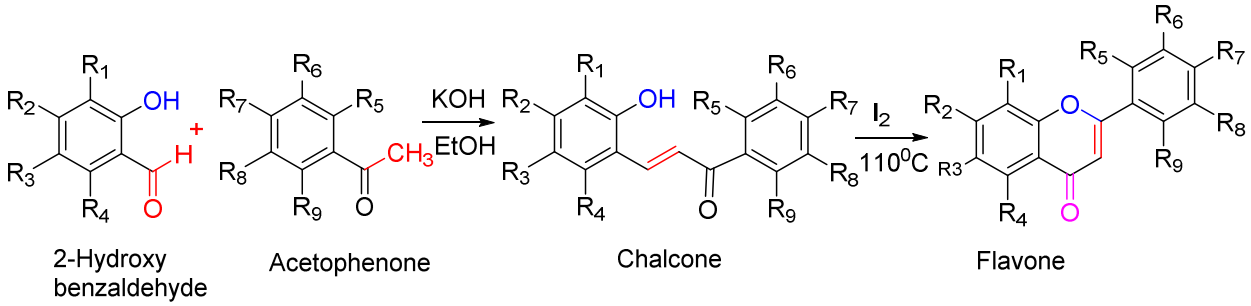
Synthetic Methodology

Previous method for the synthesis of flavones from chalcones

Scheme1.

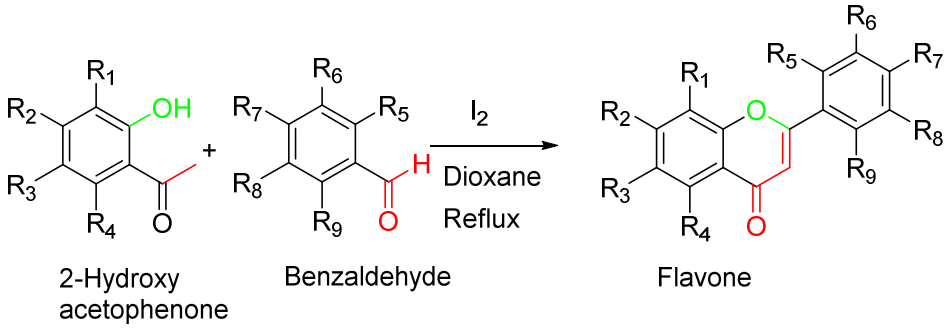


Scheme2.



Novel one pot protocol for the synthesis of flavones

Scheme3.



Scheme4.

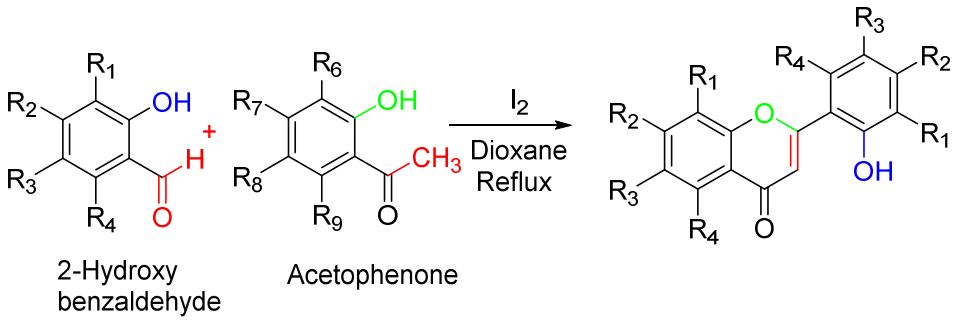


Table3. Compounds synthesized by Novel methodology

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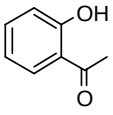
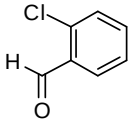
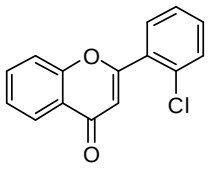
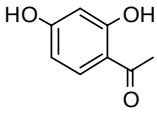
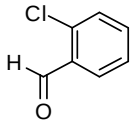
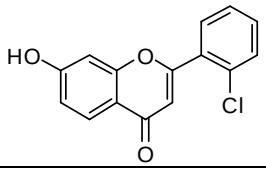
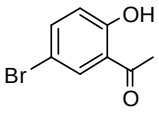
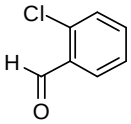
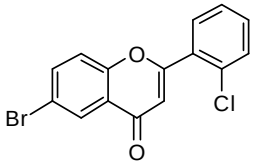
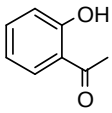
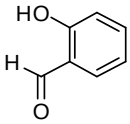
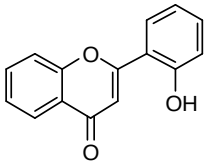
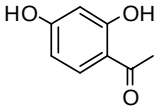
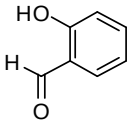
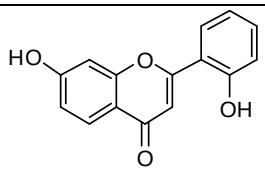
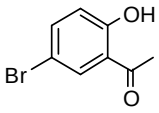
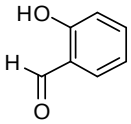
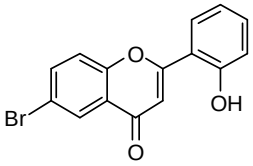
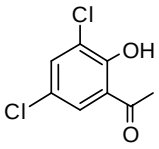
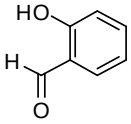
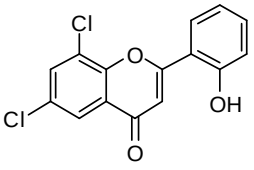
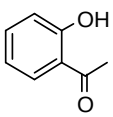
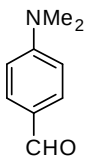
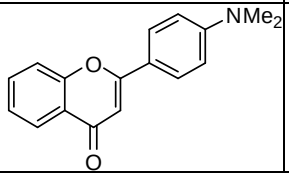
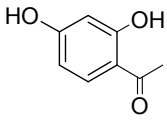
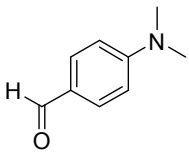
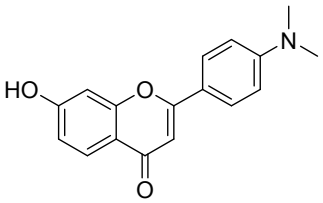
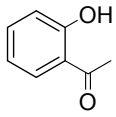
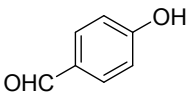
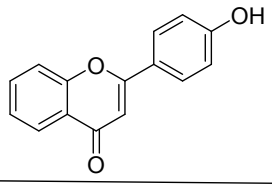
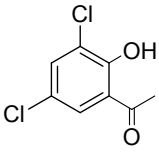
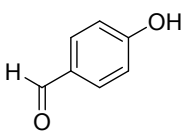
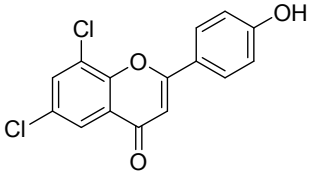
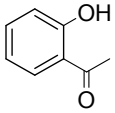
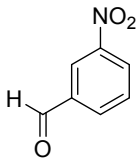
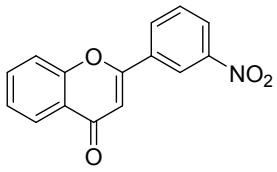
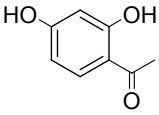
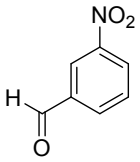
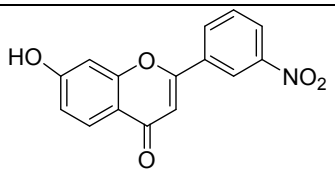
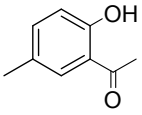
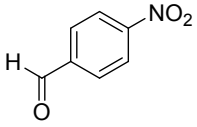
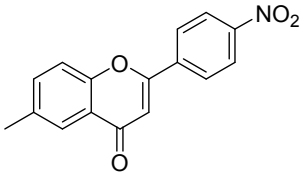
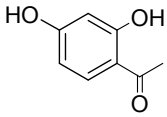
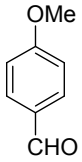
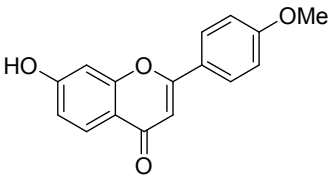
1.				2 Hrs.	60
2.				2 Hrs.	60
3.				2 Hrs.	60
4.				2 Hrs.	60
5.				2 Hrs.	60
6.				2 Hrs.	60
7.				2 Hrs.	60
8.				2 Hrs.	60

Sr.No.	Reactant 1.	Reactant 2.	Product	Time in Hrs.	% Yeild
9.				2 Hrs.	60
10.				2 Hrs.	60
11.				2 Hrs.	60
12.				2 Hrs.	60
13.				2 Hrs.	60
14.				2 Hrs.	60
15.				2 Hrs.	60

Supplementary data

Supplementary data (IR,^{1}H NMR,C^{13}) of all the compounds associated with this article is available as supplementary data

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