Synthesis of glucocorticoid-C_{60} hybrids

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There has been increasing interest in fullerene derivatives, which play important roles in biological and materials science. C_{60} hybrids containing bio-active groups have received considerable attention in recent years. The bio-active molecules that have been linked to C_{60} include sugars, peptides, amino acids and steroids [1–5]. Among such fullerene derivatives steroid-C_{60} hybrids are of great interest. This is because steroids widely exist in plants and animals and are crucial in their life process.

Hitherto, only several steroid-fullerene hybrids were synthesized by different methods [4,5]. In spite of the progress, glucocorticoid-fullerene hybrids have not been synthesized. Glucocorticoid, as a type of steroid, has both anti-inflammation and immunosuppression activities. C_{60} also has many useful bioactivities per se [6]. The combination of these two kinds of molecules might bring some beneficial effects to development of new pharmaceuticals. In this letter, we report for the first time the synthesis of five glucocorticoid-C_{60} hybrids (C_{60}-cortisone, C_{60}-hydrocortisone, C_{60}-prednisone, C_{60}-prednisolone, C_{60}-dexamethasone) by a simple method. The hybrids were also characterized by their ^{1}HNMR, ^{13}CNMR, FTIR, UV–vis and MALDITOF-MS spectra.

Methanofullerene carboxylic acid, one of the reactive derivatives of C_{60} [7], has been widely used for the formation of various methanofullerene carboxylic acid esters and amides upon treatment with alcohols and amines in the presence of a coupling reagent. Here we use the methanofullerene carboxylic acid as the active intermediate to link glucocorticoids to the C_{60} molecule in the presence of the coupling reagent.

The synthesis of glucocorticoid-C_{60} hybrids accomplished by the convergent strategy outlined in Fig. 1 is of very similar, The methanofullerene carboxylic acid slightly dissolved in chloroform was afforded in high yield through the sulfonium ylide addition to C_{60} and subsequent hydrolysis. To the chloroform solvents containing the partly-dissolved methanofullerene carboxylic acid, DCC, DMAP and glucocorticoids were added. The solutions were purged with N_2 for 5 min and then stired for 7 days in the dark at room temperature. After that, we observed transparent red solutions with some white solid DCU appearing on the sides of the flasks. The terminal products were purified by column chromatographer. Note that methanofullerene carboxylic acid cannot be completely dissolved in chloroform, the obtained transparent solutions suggest that the terminal products have better solubilities in chloroform than their parent molecule, methanofullerene carboxylic acid (Table 1).

All hybrids were characterized by their ^{1}HNMR, ^{13}CNMR, MALDITOF-MS, FTIR and UV–vis spectra. The ^{1}HNMR spectra were all consistent with the proposed structures. The ^{1}HNMR spectra of the five hybrids showed that the 21-H of the glucocorticoids shifted from 4.5 to 5.3 ppm because of the production of ester bonds, and the coupling constants increased from -20 to -17.5 Hz. At the same time the proton on the methylene of methanofullerene carboxylic acid shifted from 5.1 to 4.9 ppm for the same reason. The ^{13}CNMR spectra of the five hybrids showed the carbon resonances of the ester ketone bonds at 165 ppm. The FT-IR spectra showed ester ketone absorption bands at 1721–1728 cm^{-1} and framework absorption bands of C_{60} at 1427, 1183, 575, 525 cm^{-1}. The UV absorption spectra of the five hybrids in this study showed sharp absorption at 430–435 nm, which had been proposed to be characteristic of closed (6,6)-bridged fullerenes [8]. The MALDITOF-MS spectra all showed peaks at m/z 720 for C_{60}^+, m/z 733 for $[C_{60}\ CH]^+$, and some showed peaks at m/z 778 for $[C_{60}\ CHCOOH]^+$. Additionally, C_{60}-dexamethasone hybrid was also characterized by the ^{19}FNMR spectrum, which showed the same chemical shift of the F atom at the -165.56 ppm as that of dexamethasone. All the spectra revealed that the 21-OH reacted with methanofullerene carboxylic acid affording the hybrids containing newly-created ester bonds.

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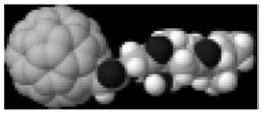
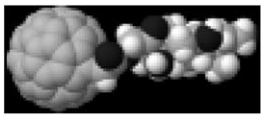
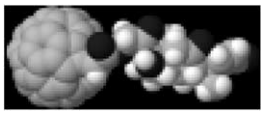
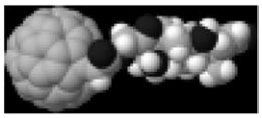
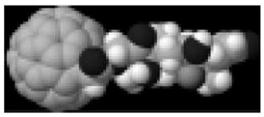
Table 1
Synthesis of C_{60}-glucocorticoid hybrids

Number	Compound	Substitute group			Computer-generated structure
		$C_{1,2}$	9α	11β	
1	C_{60}-cortisone	Single bond	H	O	
2	C_{60}-hydrocortisone	Single bond	H	OH	
3	C_{60}-prednisone	Double bond	H	O	
4	C_{60}-prednisolone	Double bond	H	OH	
5	C_{60}-dexamethasone	Double bond	F	OH	

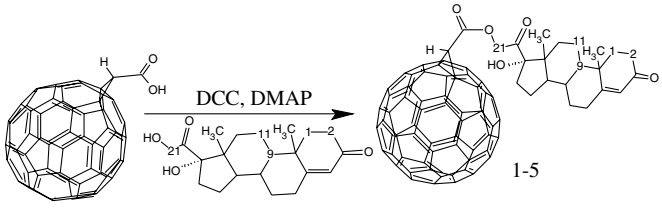


Fig. 1. Synthesis of C_{60}-glucocorticoid hybrids.

In conclusion, we successfully linked five glucocorticoids to C_{60} by a simple method. Because these five glucocorticoids have excellent pharmaceutical effects, thus produced hybrids might show new useful activities. In due course their pharmaceutical effects will be tested in our laboratory.

Appendix A. Supplementary data

Experimental section and spectral data of the five glucocorticoid-C_{60} hybrids. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carbon.2005.08.024.

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