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Comparative Crystallographic Analysis of Some Photoactive Furanocoumarins and Role of C-H...O, C-H... π & π ... π Interaction in Their Supramolecular Structure

Bandhan Sharma*

Department of Physics, Government Gandhi Memorial Science College, Jammu 180 001, India

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The compounds taken in this paper to make a comprehensive review are imperatorin, phellopterin, rutaretin, marmesin and bergapten. The aim of this research paper is to confirm the aromatic character of these compounds and to find the different type interactions responsible to assemble the molecules into supramolecular structure. The pyrone moiety of all these molecules is perfectly planar with maximum deviation of 0.009(2)Å. In all the crystals, molecules are linked by C-H...O hydrogen bonds, forming a three dimensional framework. Different structural motifs (chains, dimmers, rings, etc.) bonded with C-H... π and π ... π interactions are analysed, which leads them into supramolecular structures.

Keywords: Furanocoumarins, Photoactive, X-ray diffraction, Supramolecular structure, Pyrone ring, Hydrogen bonding

1 Introduction

The photochemical behaviour in furanocoumarins is generally attributed due to the carbonyl stretching (C=O) in the pyrone moiety of coumarin nucleus¹. The derivatives of coumarins usually occur as secondary metabolites present in seeds, roots and leaves of many plant species. A wide spectrum of biological activity of coumarin compound is known e.g., antithrombotic effect, vasodilating effect on vessel, reduction on blood pressure, antispastic and photosensitising effect². These coumarin have also used in the treatment of human immunodeficiency disease. Therefore, these compounds are widely used in the field of medicine.

The compound of imperatorin was isolated by column chromatography using silica gel and n-hexane. Several fractions were collected. The fractions eluted with n-hexane: EtoAc (9:1) mixture gave a fluorescent compound homogeneous on TLC plate, further purified by preparative TLC. Recrystallized from MeOH yielded pale yellow crystals (50 mg) identified as imperatorin on the basis of UV, IR, NMR and Mass. Phellopterin has been isolated from the roots of *Heracleum thomsoni* from Leh and Ladakh Region of Jammu and Kashmir State of India³. Dried and powdered roots (2 kg) of *Heracleum thomsoni* were extracted with petroleum ether in a soxhlet extraction apparatus for 24 h. It was obtained from petroleum ether: ethyl acetate (9:1) eluate on repeated crystallization. Rutaretin has been isolated

from the seeds of *Apium graveolens*, a weed cultivated in several parts of India. The seeds of this plant are valuable flavouring agents and are widely used in the Ayurvedic and Unani system of medicines for the treatment of bronchitis, asthma and also as household remedy for rheumatism and gout⁴. The bergapten was isolated from the herb *T. Stictocarpum*. This compound have absorption bands in the near UV region due to the presence of conjugated double bonds, and exhibit photomutagenic⁵ and photocarcinogenic properties, binding with purine bases of DNA in living cells to yield photoadducts. Marmesin was isolated from the stem bark of *Aegle marmelos*. Dried and powdered stem bark (1 kg) of *Aegle marmelos* was extracted with methanol at room temperature and the concentrated extract (55 g) was chromatographed over a column of silica gel. The chemical structures of all the five molecules are present in Fig. 1.

2 Experimental Details

The single crystals of compounds were obtained by slow evaporation technique using n-hexane, mixture of acetone and petroleum ether and acetone as solvents. A transparent needle shaped single crystal of all the compounds with dimensions (0.3×0.1×0.1) mm was mounted on the Enraf-Nonius CAD-4 diffractometer for automatic intensity data collection by using MoK α radiation ($\lambda=0.71073$ Å). $\omega/2\theta$ scan mode was employed for the data collection with θ -range (4.01 to 69.94°) for imperatorin, (2.04 to 28.23°) for phellopterin, (2.14 to 24.96°)

*Corresponding author: (E-mail: bandhansharma79@gmail.com)

for rutaretin, (5.72 to 69.9°) for marmesin and (2.8 to 25.4°) for bergapten. A total of 5926 reflections were recorded in case of imperatorin and out of which 5350 were found to be unique ($0 \leq h \leq 13$, $-14 \leq k \leq 14$, $-14 \leq l \leq 14$), and 4657 were considered to be observed

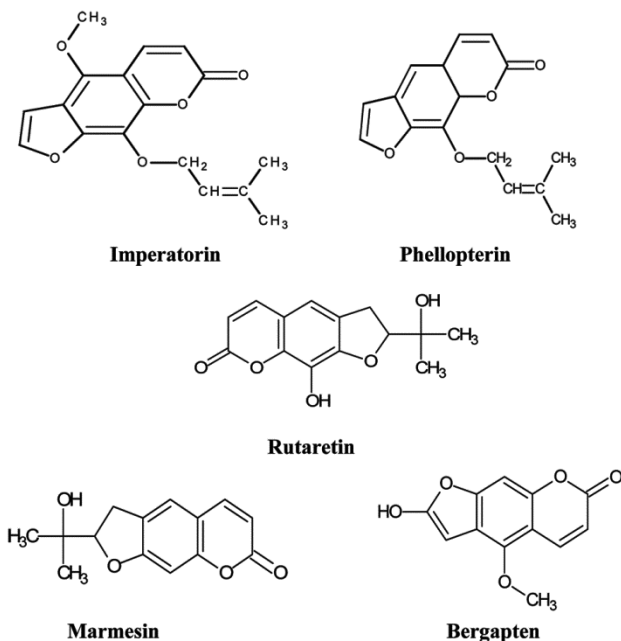


Fig. 1 — Chemical structures of the molecules.

[$F_o > 4\sigma(F_o)$]. In case of phellopterin, 6087 reflections were recorded and out of which 2586 were found to be unique ($-10 \leq h \leq 11$, $-11 \leq k \leq 11$, $-14 \leq l \leq 14$), 2549 were considered to be observed [$F_o > 4\sigma(F_o)$]. In case of rutaretin 4258 reflections were recorded and out of which 2379 were found to be unique ($-35 \leq h \leq 36$, $-11 \leq k \leq 12$, $-9 \leq l \leq 9$), 2216 were considered to be observed [$F_o > 4\sigma(F_o)$]. In case of marmesin 1200 reflections were recorded and out of which 1199 were found to be unique ($-6 \leq h \leq 6$, $0 \leq k \leq 16$, $0 \leq l \leq 9$), 1184 were considered to be observed [$F_o > 4\sigma(F_o)$]. In case of bergapten 7096 reflections were recorded and out of which 7096 were found to be unique ($-4 \leq h \leq 4$, $-17 \leq k \leq 17$, $-20 \leq l \leq 20$), 3811 were considered to be observed [$F_o > 4\sigma(F_o)$]. The structures of all the compounds were determined by SHELXS97 Software⁶. Full matrix least square refinement of all non-hydrogen atoms including their corresponding thermal parameters was carried out using SHELXL97 software⁷. The final cycle of refinement with anisotropic thermal parameters for non-hydrogen atoms converged R-factor at 0.0431 for imperatorin, 0.059 for phellopterin, 0.0356 for rutaretin, 0.0523 for marmesin and 0.080 in case of bergapten. Atomic scattering factor were taken from International Tables for Crystallography (1992, Vol. C Tables 4.2.6.8 and 6.1.1.4). The crystallographic data are listed in Table 1.

Table 1 — Crystal data and structure refinement details.

| | Imperatorin | Phellopterin | Marmesin | Rutaretin | Bergapten |
|-----------------------------|--|--|---|---|--|
| Crystal description | Transparent needles | Transparent needles | Transparent rectangular | Transparent needles | Transparent needles |
| Empirical formula | C ₁₆ H ₁₄ O ₄ | C ₁₇ H ₁₆ O ₅ | C ₁₄ H ₁₄ O ₄ | C ₁₄ H ₁₆ O ₆ | C ₁₂ H ₈ O ₄ |
| Formula weight | 270.27 | 300.3 | 246.25 | 280.27 | 216.18 |
| Crystal size (mm) | 0.3×0.1×0.1 | 0.3×0.1×0.1 | 0.4×0.2×0.1 | 0.3×0.1×0.1 | 0.4×0.08×0.02 |
| Wavelength | 1.54178 Å | 0.71073 Å | 1.5418 Å | 0.71070 Å | 0.71073 Å |
| Unit cell dimensions | a=11.1150(10)Å, b=11.8240(10)Å, c=11.9290(10)Å, α=64.90(1)°, β=83.53(1)°, γ=89.25(1)° | a=8.431(3)Å, b=8.947(3)Å, c=11.125(4)Å, α=64.11(5)°, β=71.13(5)°, γ=78.04(5)° | a=5.721(1)Å, b=13.810(1)Å, c=7.864(1)Å, β=100.39(1)° | a=24.616(8)Å, b=8.186(3)Å, c=6.632(2)Å, β=103.99(2)° | a=3.8486(8)Å, b=14.676(2)Å, c=16.866(3)Å, β=92.12(2)° |
| Crystal system | Triclinic | Triclinic | Monoclinic | Monoclinic | Monoclinic |
| Space group | P1 | P1 | P2 ₁ | C2 | P2 ₁ /C |
| Volume | 1409.6(2) Å ³ | 737.9(4) Å ³ | 611.1(1) Å ³ | 1296.7(7) Å ³ | 952.0(3) Å ³ |
| Z. Calculated density | 4, 1.274 Mg/m ³ | 2, 1.352Mg/m ³ | 2, 1.338Mg/m ³ | 4, 1.436Mg/m ³ | 4, 1.436Mg/m ³ |
| F(000) | 568 | 316 | 260 | 592 | 448 |
| Index ranges | 0 ≤ h ≤ 13, -14 ≤ k ≤ 14, -14 ≤ l ≤ 14 | -10 ≤ h ≤ 11, -11 ≤ k ≤ 11, -14 ≤ l ≤ 14 | -6 ≤ h ≤ 6, 0 ≤ k ≤ 16, 0 ≤ l ≤ 9 | -35 ≤ h ≤ 36, -11 ≤ k ≤ 12, -9 ≤ l ≤ 9 | -4 ≤ h ≤ 4, -17 ≤ k ≤ 17, -20 ≤ l ≤ 20 |
| Reflections collected | 5926 | 6087 | 1200 | 14258 | 7096 |
| Reflections unique | 5350 | 2586 | 1199 | 2379 | 7096 |
| Goodness-of-fit on F2 | 1.052 | 1.198 | 1.080 | 1.081 | 0.86 |
| R-factor | 0.0431 | 0.059 | 0.0523 | 0.0356 | 0.080 |
| Largest diff. Peak and hole | 0.23 and -0.16 eÅ ⁻³ | 0.20 and -0.26 eÅ ⁻³ | 0.246 and -0.233 eÅ ⁻³ | 0.41 and -0.28 eÅ ⁻³ | 0.19 and -0.22 eÅ ⁻³ |

3 Results and Discussion

The bond distances for non-hydrogen atoms in the pyrone moiety of all molecules are presented in Table 2. An ORTEP view of all the molecules with atomic numbering scheme is in Fig. 2. The geometrical calculations were performed by using PARST⁸ and PLATON⁹. The bond distances and bond angles for all the compounds are in good agreement with the corresponding values of the analogous structures¹⁰⁻¹⁷. All the compounds in our present study, show intra and inter C-H...O bonding and are presented in Table 3. The molecules are linked to one another through CH...O hydrogen bonds and hydrogen-bonding network is shown in Fig. 3. The C2-H2...O14 and C5-H5...O1 intermolecular hydrogen interactions result into a linear chain like configuration. Thus, they form a three dimensional

networking intermolecular C2-H2...O14 interaction, C2 at (x, y, z) acts as hydrogen donor to O14 at (-1+x, 1+y, z) where as in case of C5-H5...O1 intermolecular interactions, O1 at (1+x, y, z) acts as hydrogen acceptor in phellopterin. In case of imperotrin, the bifurcated acceptor O2 is involved with two intermolecular interactions in molecule-I whereas in molecule-II, it makes one intermolecular and one intramolecular interaction. Atoms C4 and C12 act as donor atoms in all the above mentioned weak interactions. In the benzopyran ring, the mean bond distances for C6-C7 and C7-O8 for all the present compounds are 1.39(5) Å and 1.367(4) Å respectively, indicating that the electrons are delocalized in the ring with the carbonyl group acting as the electron withdrawing group. This is supported by the fact that benzopyran ring is planar with

Table 2 — Bond distances for non hydrogen atoms of the pyrone moiety.

| Imperatorin | | | | Bergapten | | | |
|--------------|-----------|-----------|-----------|-----------|-----------|-------|-----------|
| O1-C2 | 1.381(2) | O1'-C2' | 1.386(2) | O1-C1 | 1.369 (5) | C2-C3 | 1.327 (6) |
| C2-O2 | 1.209(2) | C2'-O2' | 1.208(2) | O1-C2 | 1.386 (5) | C5-C6 | 1.345(4) |
| C2-C3 | 1.438(3) | C2'-C3' | 1.433(3) | O2-C7 | 1.385 (4) | C4-C5 | 1.394 (6) |
| C3-C4 | 1.337(3) | C3'-C4' | 1.336(3) | O2-C11 | 1.383 (5) | C5-C6 | 1.391 (5) |
| C4-C10 | 1.4441(2) | C4'-C10' | 1.443(2) | O3-C5 | 1.365 (4) | C6-C7 | 1.398 (5) |
| C9-C10 | 1.403(2) | C9'-C10' | 1.402(2) | C1-C4 | 1.393 (6) | C6-C9 | 1.442 (5) |
| O1-C9 | 1.386(2) | O1'-C9' | 1.380(2) | C7-C8 | 1.374 (5) | | |
| Phellopterin | | Rutaretin | | C9-C10 | 1.325 (5) | | |
| O8-C13 | 1.373(2) | O8-C13 | 1.387(15) | C1-C11 | 1.435 (5) | | |
| C12-C13 | 1.401(2) | C12-C13 | 1.406(19) | Marmesin | | | |
| C5-C6 | 1.329(3) | C5-C6 | 1.358(2) | C5-C12 | 1.423(4) | | |
| C5-C12 | 1.433(2) | C5-C12 | 1.429(2) | C6-C7 | 1.443(5) | | |
| C6-C7 | 1.435(3) | C6-C7 | 1.229(16) | C7-O7 | 1.214(4) | | |
| C7-O14 | 1.198(3) | C7-O14 | 1.368(18) | C7-O8 | 1.370(4) | | |
| C7-O8 | 1.385(2) | C7-O8 | 1.358(2) | O8-C13 | 1.374(3) | | |

Table 3 — Geometry of C-H...O hydrogen bonds.

| C-H...O | H...O(Å) | C...O(Å) | C-H...O(°) | C-H...O | H...O(Å) | C...O(Å) | C-H...O(°) |
|-----------------|----------|----------|------------|-----------------------------|----------|----------|------------|
| Imperatorin | | | | Bergapten | | | |
| C4-H4...O2' | 2.54 | 3.34 | 137.8 | C2-H2...O3 ⁱ | 2.49 | 3.406 | 170 |
| C4'-H4'...O2 | 2.58 | 3.46 | 159.7 | C3-H3...O4 ⁱⁱ | 2.57 | 3.484 | 170 |
| C11-H11...O14' | 2.64 | 3.35 | 139.3 | C10-H10...O4 ⁱⁱⁱ | 2.51 | 3.387 | 158 |
| C12-H12...O2 | 2.36 | 3.27 | 172.4 | C12-H12A...O4 ⁱⁱ | 2.44 | 3.376 | 165 |
| C12'-H12'...O2' | 2.34 | 3.32 | 178.8 | Marmesin | | | |
| Phellopterin | | | | C2-H2...Cg1 ⁱ | 2.721 | 3.703 | 169 |
| C2-H2...O14 | 2.41 | 3.16 | 137.5 | C3-H32...O17 | 2.45 | 2.944 | 108 |
| C5-H5...O1 | 2.59 | 3.30 | 133.7 | C5-H5...O17 ⁱⁱⁱ | 2.51 | 3.314 | 156 |
| Rutaretin | | | | | | | |
| C18-H18...O1 | 2.84 | 3.38 | 142.4 | | | | |
| O15-H15...O19 | 2.64 | 3.47 | 168.5 | | | | |
| O20-20A...O14 | 2.28 | 3.31 | 171.3 | | | | |

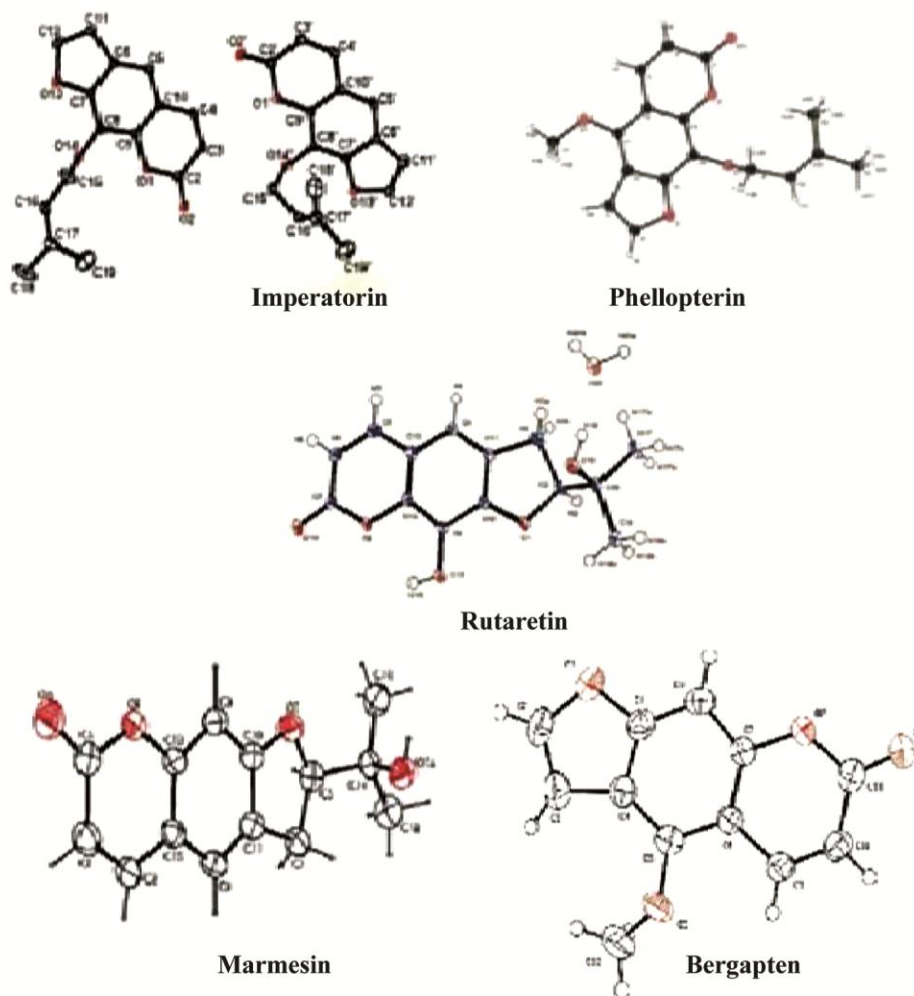


Fig. 2 — Ortep view of the molecules.

maximum deviation of 0.009(2) Å. The widening of the angle O7–C7–O8 is another commonly occurring feature which is usually observed in coumarin systems and the large value of this angle is attributed to the lone-pair interactions between O7 and O8. The supramolecular structures of these furanocoumarins are dictated by two intermolecular hydrogen bonds. The stronger of these two hydrogen bonds (O17–H17O...O7) gives rise to a chain running parallel to the [010] direction in case of marmesin. The hydroxyl-methylethyl chain located at C2 of rutaretin is inclined more towards O1 (108.4°) than C3 (114.9°) which might be the reason for the formation of C18–H18...O1 intermolecular interaction. Both the hydroxyl groups of the molecule located at C9 and C16 are linked through a linear intermolecular hydrogen bond O15–H15...O19 at (–x, y, 2–z) in which O19 acts as proton acceptor in case of bergapten.

There is one C–H... π (arene) hydrogen bond with H...centroid distance of less than 3.0 Å which serves to link all of the sheets into a single three dimensional framework. Atom C2 in the molecule at (x, y, z) acts as a hydrogen-bond donor to the benzene ring in the molecule at (x + 1, y, z).

The overall X–H...A range in case of intermolecular interactions comes out to be between 2.28 to 2.84, thus making these interactions fall under the category of strong to weak interactions as suggested by Desiraju and Steiner in an International monogram on crystallography in 1999¹⁸. The three-dimensional framework of the compounds forms C–H... π and π ... π interactions between the pyrone and phenyl rings as shown in Fig. 3. The average value of bond distances C2=O2 and C3=C4 in the pyrone ring of coumarin moiety for all the five coumarin structure taken in this work are 1.211 and 1.34 Å which are very close to

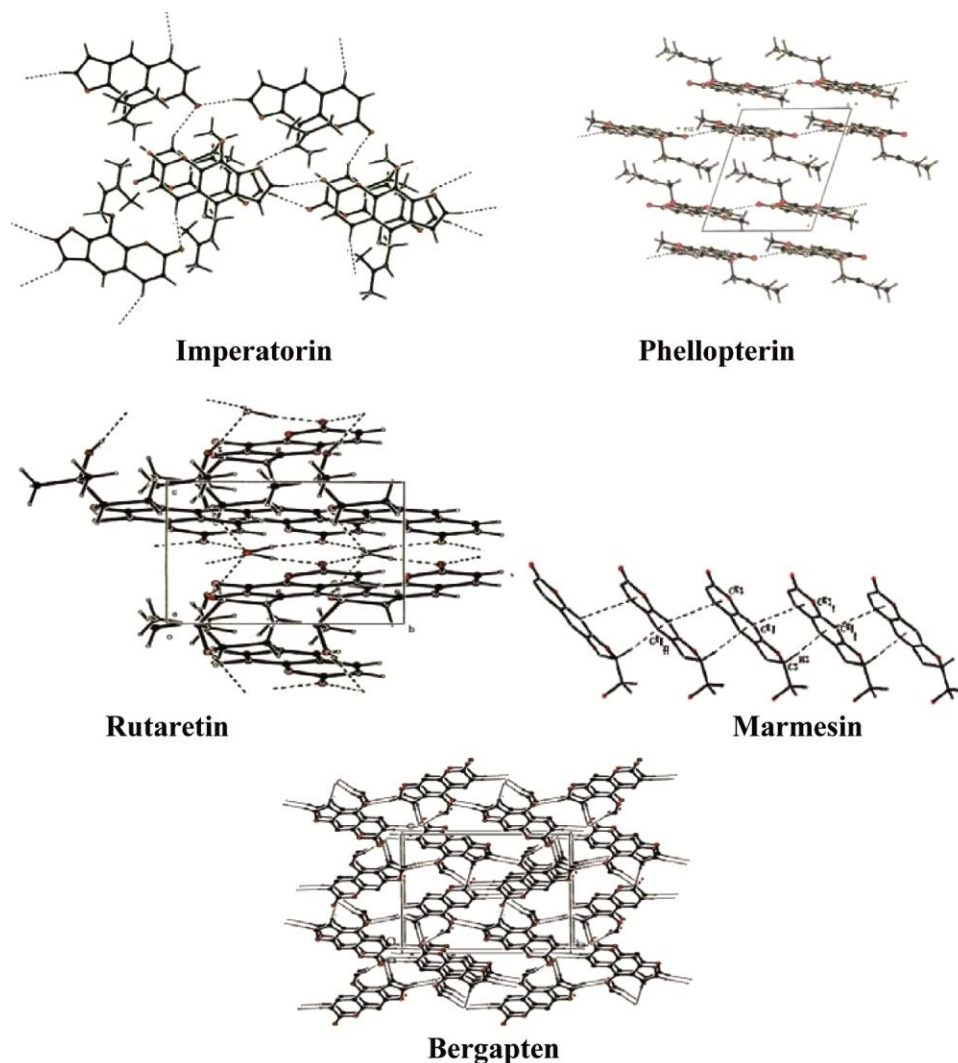


Fig. 3 — Three-dimensional framework of the C-H... π and π ... π interactions.

their standard values. These values might be the reason for their photoactivity.

The advantage of the used technique is that it gives very accurate molecular structure of the crystal which can be analyzed by the value of R-factor. That's why this technique is used in the Pharmaceuticals lab, Forensics lab and Microelectronics lab. On the other hand this technique has a disadvantage that a homogeneous and single crystal material is the best to classify unknown.

4 Conclusions

The dihedral angle between the pyrone and benzene rings for all the compounds is about $0.3 (1)^\circ$ which indicates that there is a perfect planarity in the benzopyrone moiety which confirms the aromatic characters of these compounds. The photoactivity of

furanocoumarins is due to carbonyl stretching (C=O) in the pyrone moiety of coumarin nucleus and the average value of bond distances C2=O2 and C3=C4 in the pyrone ring of coumarin moiety for all the five coumarin structure taken in this work are 1.211 and 1.34 Å. In all crystals, the molecules are linked by C-H...O hydrogen bonds forming three-dimensional network. There is also analysed π ... π interactions, which shows that π ... π stacking is an offset arrangement of the rings. All the interactions C-H... π , C-H...O, hydrogen bonds and π ... π stacking interactions play a crucial part in assembling the molecules into an organised supramolecular structure.

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