

Research article

Open Access

**R<sub>2</sub><sup>2</sup>(8) motifs in Aminopyrimidine sulfonate/carboxylate interactions: Crystal structures of pyrimethaminium benzenesulfonate monohydrate (2:2:1) and 2-amino-4,6-dimethylpyrimidinium sulfosalicylate dihydrate (4:2:2)**  
Kasthuri Balasubramani<sup>1</sup>, Packianathan Thomas Muthiah\*<sup>1</sup> and Daniel E Lynch<sup>2</sup>

Address: <sup>1</sup>School of Chemistry, Bharathidasan University, Tiruchirappalli -620 024, Tamil Nadu, India and <sup>2</sup>Faculty of Health and Life Sciences, Coventry University, Coventry CV1 5FB, UK

Email: Kasthuri Balasubramani - bala1679@yahoo.com; Packianathan Thomas Muthiah\* - tommtrichy@yahoo.co.in; Daniel E Lynch - apx106@coventry.ac.uk

\* Corresponding author

Published: 13 November 2007

Received: 5 September 2007

Chemistry Central Journal 2007, 1:28 doi:10.1186/1752-153X-1-28

Accepted: 13 November 2007

This article is available from: <http://journal.chemistrycentral.com/content/1/1/28>

© 2007 Balasubramani et al; This is an open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

## Abstract

**Background:** Pyrimethamine [2,4-diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine] is an antifolate drug used in anti-malarial chemotherapy. Pyrimidine and aminopyrimidine derivatives are biologically important compounds owing to their natural occurrence as components of nucleic acids.

**Results:** In the crystal structures of two organic salts, namely pyrimethaminium benzenesulfonate monohydrate **1** and 2-amino-4, 6-dimethylpyrimidinium 3-carboxy-4-hydroxy benzenesulfonate dihydrate **2**, pyrimethamine (PMN) and 2-amino-4,6-dimethylpyrimidine (AMPY) are protonated at one of the nitrogens in the pyrimidine rings. In both the PMN and AMPY sulfonate complexes, the protonated pyrimidine rings are hydrogen bonded to the sulfonate groups, forming a hydrogen-bonded bimolecular ring motif with graph-set notation R<sub>2</sub><sup>2</sup>(8). The sulfonate group mimics the carboxylate anion's mode of association, which is more commonly seen when binding with 2-aminopyrimidines. In compound **1**, the PMN moieties are centrosymmetrically paired through a complementary DADA array of hydrogen bonds. In compound **2**, two types of bimolecular cyclic hydrogen bonded R<sub>2</sub><sup>2</sup>(8) motifs (one involving the carboxylate group and the other involving sulfonate group) coexist. Furthermore, this compound is stabilized by intra and intermolecular O-H...O hydrogen bonds.

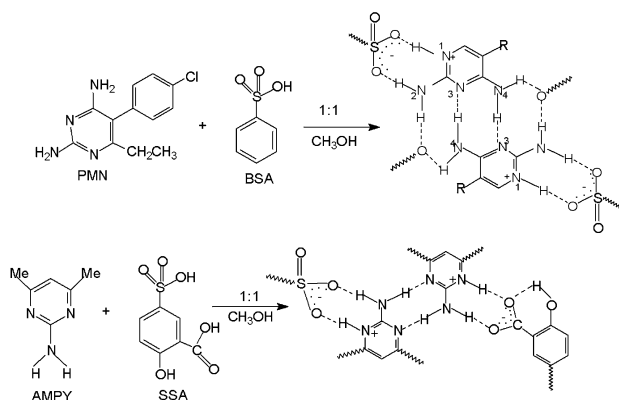
**Conclusion:** The crystal structures of pyrimethaminium benzenesulfonate monohydrate and 2-amino-4,6-dimethylpyrimidinium sulfosalicylate dihydrate have been investigated in detail. In compound **1**, the R<sub>2</sub><sup>2</sup>(8) motif involving the sulfonate group is present. The role the sulfonic acid group plays in mimicking the carboxylate anions is thus evident. In compound **2**, two types of bimolecular cyclic hydrogen bonded R<sub>2</sub><sup>2</sup>(8) motifs (one involving the carboxylate group and the other involving sulfonate group) coexist. In both the compounds base pairing also occurs. Thus homo and hetero synthons are present.

## Background

Intermolecular interactions and hydrogen bond motifs that occur repeatedly in crystal structures are called supramolecular synthons. Synthons are the recognition motifs between building blocks that can be used to propagate networks or supramolecular assemblies [1]. Hydrogen bonding patterns involving sulfonate groups in biological systems and metal complexes are of current interest [2-6]. Such interactions can be used for designing supramolecular architectures. Numerous hydrogen-bonding patterns of aminopyrimidine-carboxylate interactions [7,8] have been reported in the literature. Recently, different types of hydrogen-bonding motifs in sulfonate salts have been examined using the Cambridge Structural Database (CSD) [9].

The 2,4-diaminopyrimidine antifolates have been reviewed in the literature [10]. The different types of hydrogen-bonding patterns present in diaminopyrimidine-carboxylates [11] and aminopyrimidine complexes, such as pyrimethamine (PMN) hydrogen maleate, PMN hydrogen succinate, PMN hydrogen phthalate [12], PMN formate [13], PMN sulfosalicylate monohydrate [14], PMN *o*-nitrobenzoate, PMN *m*-nitrobenzoate, PMN *p*-nitrobenzoate [15], trimethoprim (TMP) benzenesulfonate monohydrate, TMP sulfanilate monohydrate, TMP *p*-toluene sulfonate and TMP sulfosalicylate dehydrate [16] 2-amino-4,6-dimethylpyrimidine (AMPY) hydrogen sulfate [17], 2-amino-4,6-dimethylpyrimidine-cinnamic acid [18], and 2-amino-4,6-dimethylpyrimidine-4-hydroxy benzoic acid [19] co-crystal structures, have been reported from our laboratory.

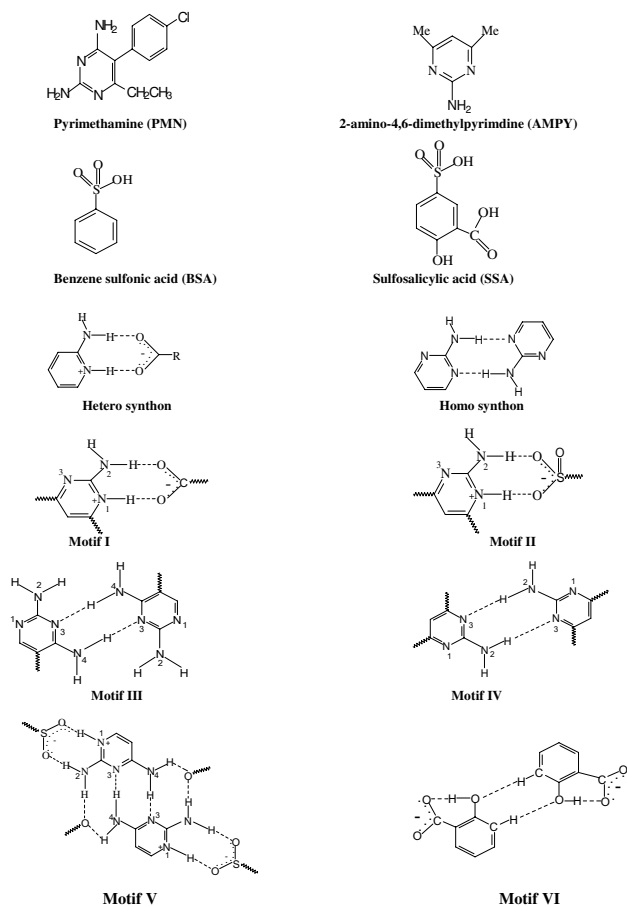
Pyrimethamine [2,4-diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine] is an antifolate drug [20] used in anti-malarial chemotherapy. The drug binds with great affinity to the bacterial enzyme dihydrofolate reductase (DHFR) [21]. PMN is also used along with other drugs for the treatment of opportunistic infections in patients with AIDS [22]. 2-aminopyrimidine and its derivatives are of particular interest as adduct formers because of their ability to form stable hydrogen-bonded chains via their stereochemically associated amine group and the ring N atoms [23]. Hydrogen bonding plays a key role in molecular recognition [24] and crystal engineering [25]. The present study deals with hydrogen bonding, the nature of hydrogen-bonded arrays and the supramolecular synthons present in the aminopyrimidine-sulfonate salts (Scheme 1).



**Scheme 1:** Hydrogen-bonded arrays and the supramolecular synthons present in the aminopyrimidine-sulfonate salts

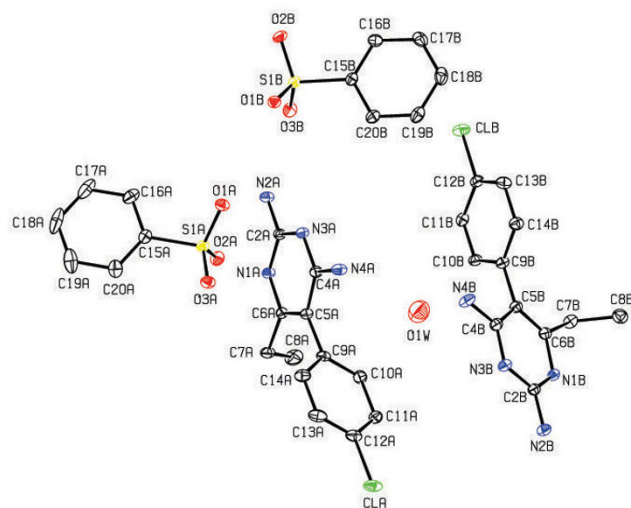
## Results and discussion

The three dimensional supramolecular architectures in such compounds can be analyzed in terms of various components such as motifs, chains, stacking interactions *etc.* The schematic representation of the hydrogen-bonded motifs observed in this study is shown in Figure 1. In the crystal structure of compound 1, the asymmetric unit contains a pair of pyrimethaminium (PMN) cations (A and B), benzenesulfonate anions (A and B) and a water molecule as shown in Figure 2. In compound 2, four molecules of 2-amino-4,6-dimethylpyrimidinium (AMPY) cations (A, B, C and D), two molecules of 3-carboxy-4-hydroxy benzenesulfonate (sulfosalicylate) anions (A and B), and two water molecules constitute the asymmetric unit (Figure 3). The PMN moieties are protonated at N1, leading to an enhancement of the internal bond angles at N1 [C2A-N1A-C6A 121.6(2)° and C2B-N1B-C6B 121.5(2)° in compound 1]. The angles are larger than the values observed in neutral pyrimethamine [116.25(18)° (molecule A) and 116.09(18)° (molecule B)] [26]. In compound 2, protonation of the pyrimidine base on the N1 site is reflected in the larger bond angle, as compared with the unprotonated site. The angles at the protonated N1 atom are C2A-N1A-C6A 121.85(17)°; C2B-N1B-C6B 121.93(17)°; C2C-N1C-C6C 121.64(18)° and C2D-N1D-C6D 121.73(18)°. The similar angles at the unprotonated N3 nitrogen are 117.20(17)° (molecule A), 117.52(17)° (molecule B), 117.35(18)° (molecule C) and 117.68(18)° (molecule D). The geometry of the pyrimidine cation agrees with that of other pyrimidine cations reported in the literature [27]. In compound 1, the dihedral angles between the 2,4-diaminopyrimidine and the *p*-chlorophenyl are 78.50(12)° (molecule A) and 73.20(12)° (molecule B). These values are close to the values observed in the modelling studies carried out on the dihydrofolate reductase-pyrimethamine (DHFR-PMN) complexes [28]. The important torsion angles governing the orientation of the 6-ethyl group are C5A-C6A-



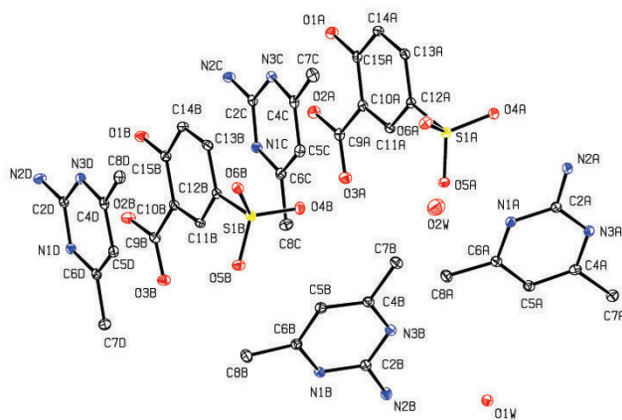
**Figure 1**  
The schematic diagram for the various hydrogen-bonded motifs observed in compounds 1 and 2.

C7A-C8A ( $-105.3(3)^\circ$  in molecule A) and C5B-C6B-C7B-C8B ( $110.4(3)^\circ$  in molecule B). The lengths of the bonds connecting the pyrimidine and phenyl rings are  $1.493(3)\text{\AA}$  (molecule A) and  $1.496(3)\text{\AA}$  (molecule B). These values are in close agreement with those observed in the crystal structure of metoprine ( $1.495\text{\AA}$  in molecule A and  $1.478\text{\AA}$  in molecule B) [29]. In compounds 1 and 2, the sulfonate group mimics the association of the carboxylate moiety and makes a hydrogen-bonded ring of graph-set notation  $R_2^2(8)$  with the PMN and AMPY cations. The hydrogen-bonding geometry of the N-donors to the sulfonate group gave a mean value for the N-H...O hydrogen bond distances involving sulfonates that was slightly longer in range when compared with the carboxylate O atoms indicating that sulfonates form longer and weaker hydrogen bonds with N-donors than carboxylates. These trends are also observed in the present investigation, as indicated in Table 1. The hydrogen bonds formed between the sulfonates and the N-donors were generally linear [30]. In compound 1, the protonated pyrimeth-



**Figure 2**  
The ORTEP view of the asymmetric unit of the compound 1 (Hydrogen atoms are omitted for clarity).

aminium (N1A and N1B) cations interact with the (O3A and O2B) oxygen atoms of the sulfonate anions through N-H...O hydrogen bonds (Heterosynthon) forming an eight membered ring motif  $R_2^2(8)$  [31-33] (motif II). The pyrimethaminium cations are centrosymmetrically paired through N4-H...N3 hydrogen bonds (Homosynthon) involving the 4-amino group and the N3 atom of the unprotonated pyrimidine to form the ring motif  $R_2^2(8)$  (motif III) (Table 1). In addition to the base pairing, one of the sulfonate oxygen atoms (O1B and O1A) (a hydrogen bond acceptor) bridges the 4-amino and the 2-amino groups on both sides of the pairing. The combination of such base-pairing patterns and the further bridging of the



**Figure 3**  
The ORTEP view of the asymmetric unit of the compound 2 (Hydrogen atoms are omitted for clarity).

**Table 1: Hydrogen bonding geometry for the compounds 1 and 2**

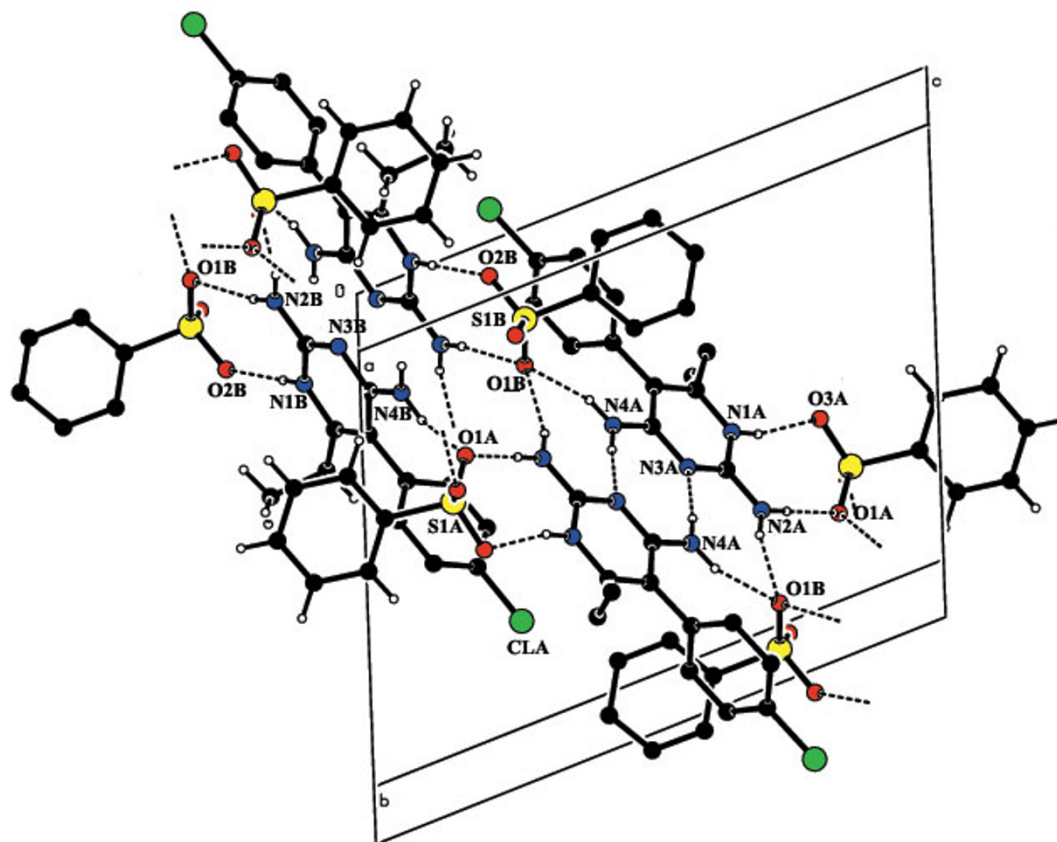
| Compound | D-H...A                         | H...A | D...A     | D-H...A |
|----------|---------------------------------|-------|-----------|---------|
| 1.       | N1A – H1A .. O3A                | 1.90  | 2.733(3)  | 164     |
|          | N1B – H1B .. O2B <sup>a</sup>   | 1.89  | 2.742(3)  | 169     |
|          | N2A – H3A .. O1B                | 2.15  | 2.980(3)  | 161     |
|          | N2B – H3B .. O2A <sup>b</sup>   | 2.00  | 2.843(3)  | 167     |
|          | N2A – H4A .. O1A                | 1.99  | 2.847(3)  | 175     |
|          | N2B – H4B .. O1B <sup>a</sup>   | 2.23  | 3.076(3)  | 168     |
|          | N4A – H5A .. N3A <sup>c</sup>   | 2.16  | 3.013(3)  | 170     |
|          | N4A – H6A .. O1B <sup>c</sup>   | 2.33  | 3.015(3)  | 137     |
|          | N4B – H6B .. O1A <sup>c</sup>   | 2.43  | 3.079(3)  | 133     |
|          | C10B – H10B .. O2A <sup>d</sup> | 2.54  | 3.364(4)  | 148     |
| 2.       | N1B–H1B1 ... O6B <sup>e</sup>   | 1.84  | 2.693 (2) | 168     |
|          | O1A–H1A ... O2A                 | 1.81  | 2.539 (2) | 147     |
|          | O1B–H1B ... O2B                 | 1.77  | 2.498 (2) | 147     |
|          | N1C–H1C ... O2B <sup>f</sup>    | 1.75  | 2.614 (2) | 179     |
|          | N1D–H1D ... O2A <sup>f</sup>    | 1.83  | 2.682 (2) | 174     |
|          | O1W–H1W ... O5B <sup>g</sup>    | 1.97  | 2.785 (2) | 139     |
|          | N1A–H1A1 ... O5A                | 1.87  | 2.722 (2) | 168     |
|          | O1W–H2W ... O6A <sup>e</sup>    | 2.08  | 2.775 (2) | 127     |
|          | N2C–H2C1 ... O3B <sup>f</sup>   | 2.05  | 2.908 (2) | 173     |
|          | N2C–H2C2 ... N3D <sup>h</sup>   | 2.16  | 3.010 (3) | 169     |
|          | N2A–H2A1 ... O1W <sup>i</sup>   | 2.10  | 2.927 (2) | 162     |
|          | N2A–H2A2 ... O4A                | 2.03  | 2.889 (2) | 172     |
|          | N2D–H2D1 ... N3C <sup>i</sup>   | 2.16  | 3.003 (3) | 165     |
|          | N2D–H2D2 ... O3A <sup>f</sup>   | 1.95  | 2.809 (2) | 173     |
|          | N2B–H2B1 ... O1W                | 2.10  | 2.933 (2) | 164     |
|          | N2B–H2B2 ... O4B <sup>e</sup>   | 2.01  | 2.871 (2) | 177     |
|          | C5A–H5A ... O4A <sup>e</sup>    | 2.51  | 3.382 (2) | 156     |
|          | C5B–H5B ... O4B                 | 2.51  | 3.352 (2) | 151     |
|          | C5B–H5B ... O5B                 | 2.58  | 3.428 (3) | 152     |
|          | C11A–H11A ... O5A               | 2.43  | 2.849 (2) | 107     |
|          | C11B–H11B ... O5B               | 2.60  | 2.946 (2) | 103     |
|          | C8D–H8D2 ... O6B                | 2.47  | 3.378 (3) | 159     |
|          | C14B–H14B ... O1B <sup>h</sup>  | 2.36  | 3.275 (3) | 169     |
|          | C7B–H7B3 ... O5A                | 2.52  | 3.421 (3) | 156     |
|          | C7A–H7A1 ... O6B <sup>j</sup>   | 2.50  | 3.458 (3) | 174     |
|          | C7D–H7D3 ... O3B                | 2.58  | 3.413 (3) | 145     |

(a) x-l, y-l, z-l; (b) x, y-l, z-l; (c) 2-x, l-y, l-z; (d) l-x, l-y, l-z; (e) x-l, y, z; (f) l-x, l-y, z; (g) l-x, l-y, l-z; (h) 2-x, l-y, z; (i) l-x, y, l-z; (j) x-l, y-l, z.

bases involved in the pairing by hydrogen bonds, leads to the formation of a linear array of four hydrogen bonds. This is called a complementary DADA array (motif V) of quadruple hydrogen-bonding patterns (D stands for hydrogen-bond donor, and A stands for hydrogen-bond acceptor). The corresponding graph-set notations are  $R_3^2(8)$ ,  $R_2^2(8)$  and  $R_3^2(8)$  (Figure 4). This type of DADA array of quadruple hydrogen bonds has been observed in some previously reported crystal structures [12].

In compound 2, two types of bimolecular cyclic hydrogen-bonded  $R_{22}(8)$  motifs (motif I and motif II) are formed. Motif I involves protonated aminopyrimidinium cations (N1A and N1B), and the 2-amino group and sulfosalicylate anions (carboxylate group) (O5A and O6B). Motif II is formed by protonated aminopyrimidinium cat-

ions (N1C and N1D), and the 2-amino group and sulfosalicylate anions (sulfonate group) (O2B and O2A). There is also base pairing via a pair of N-H...N hydrogen bonds (motif IV) involving two aminopyrimidinium molecules (cations C and D). These arrays are connected via a pair of C-H...O hydrogen bonds involving centrosymmetrically paired sulfosalicylates (B molecule) to form a supramolecular network (Figure 5). The commonly observed intramolecular hydrogen bond between the phenol -OH and carboxyl group in salicylic acid is also present in the sulfosalicylate anion (motif VI) [32]. The two sulfosalicylate (carboxylate group) oxygen atoms interact with 2-amino-4,6-dimethylpyrimidinium cations through C-H...O hydrogen bonds. The base pairing and C-H...O hydrogen bonds are arranged alternatively to form a chain (Figure 6). The two sulfosalicylate anions (O5B



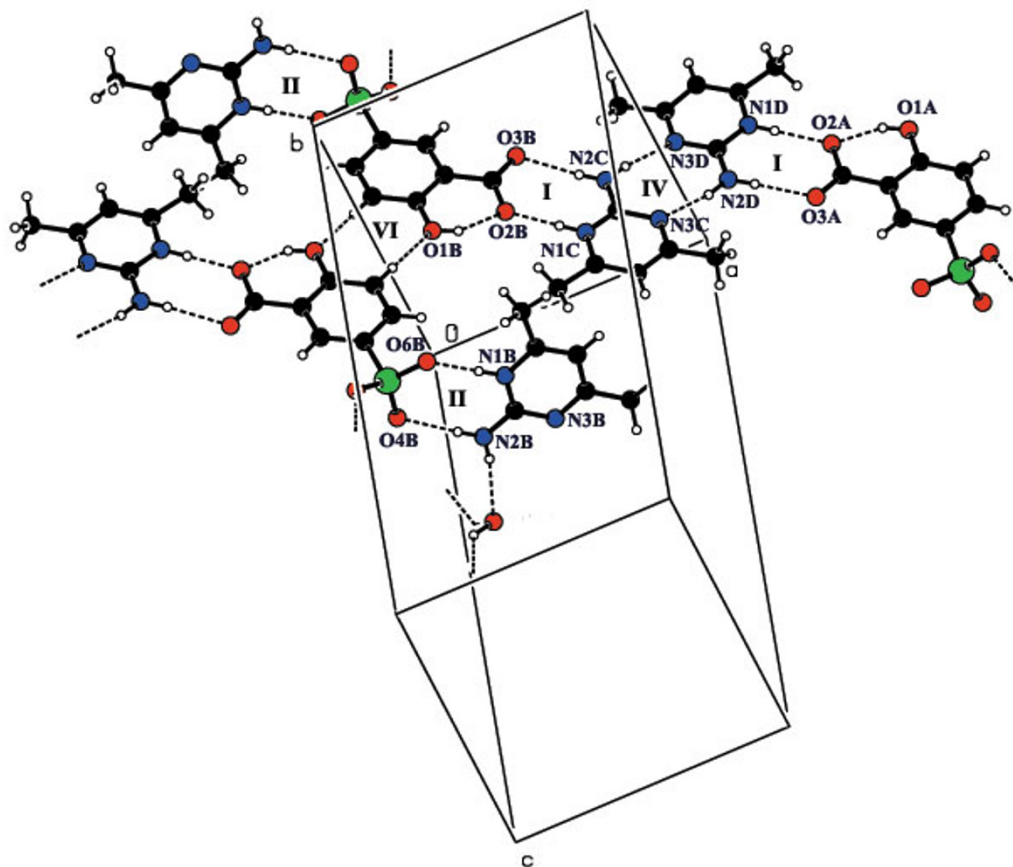
**Figure 4**  
The hydrogen-bonded DADA array in the compound 1.

and O6A) are bridged by the water molecule (O1 W) via O-H...O hydrogen bonds (Figure 7). In compound 1, PMNBSA,  $\pi$ - $\pi$  stacking interactions between benzenesulfonate molecules are observed with a perpendicular separation of 3.356Å, a centroid-to-centroid distance of 3.608(2) Å and a slip angle of 21.54° (Figure 8). In compound 2, AMPYSSA, the 2-amino-4,6-dimethylpyrimidinium cations (C), stack with sulfosalicylate anions A and B, with a perpendicular separation of 3.319Å and 3.359Å, a centroid-to-centroid distance of 3.529(11)Å and 3.554(11)Å and a slip angle of 17.49° and 19.30° respectively. A similar type of stacking is also observed between the 2-amino-4,6-dimethylpyrimidinium cation (D) and the sulfosalicylate anions (A and B), with a perpendicular separation of 3.238Å and 3.360Å, a centroid-to-centroid distance of 3.730(11)Å and 3.483(11)Å and a slip angle

of 24.13° and 19.30° respectively (Figure 9). These are typical aromatic stacking values [34].

### Conclusion

The crystal structures of pyrimethamine benzenesulfonate monohydrate and 2-amino-4,6-dimethylpyrimidine sulfosalicylate dihydrate have been investigated in detail. In compound 1, the  $R_2^2(8)$  motif involving the sulfonate group is present. The role the sulfonic acid group plays in mimicking the carboxylate anions is thus evident. In compound 2, two types of bimolecular cyclic hydrogen bonded  $R_2^2(8)$  motifs (one involving the carboxylate group and the other involving sulfonate group) coexist. In both the compounds base pairing also occurs. Thus homo and hetero synthons are present. These synthons combine to form a supramolecular network. This observation is rel-



**Figure 5**  
Hydrogen-bonding patterns involving carboxylate/sulfonate groups in compound 2 (I, II, IV and VI indicates hydrogen bonded motifs).

evant for many supramolecular architectures and crystal engineering.

#### Experimental

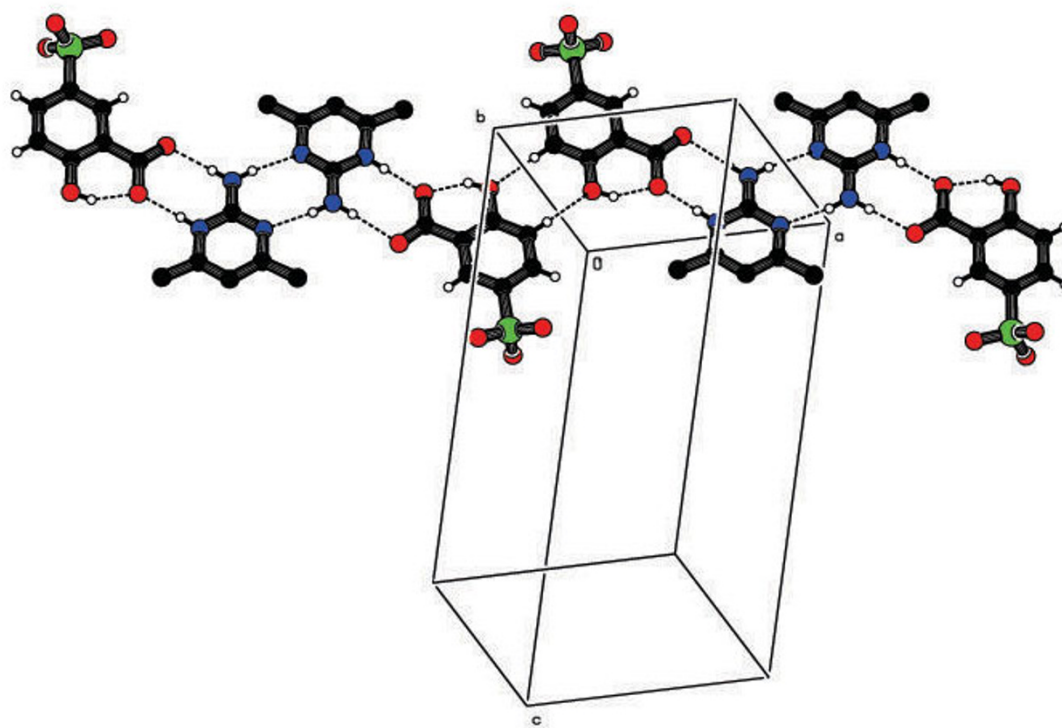
Compounds 1 and 2 were prepared by the mixing of hot methanolic solutions of PMN (62 mg, Shah Pharmachem, India) or AMPY (Aldrich) and the corresponding acids -benzene sulfonic acid (40 mg, Merck) & 3-carboxy-4-hydroxy-benzene sulfonic acid (55 mg, Merck) in 1:1 molar ratio and warming over water bath for 20 min. After a few days blocks of colourless crystals of compound 1 and 2 were obtained.

#### X-ray Crystallography

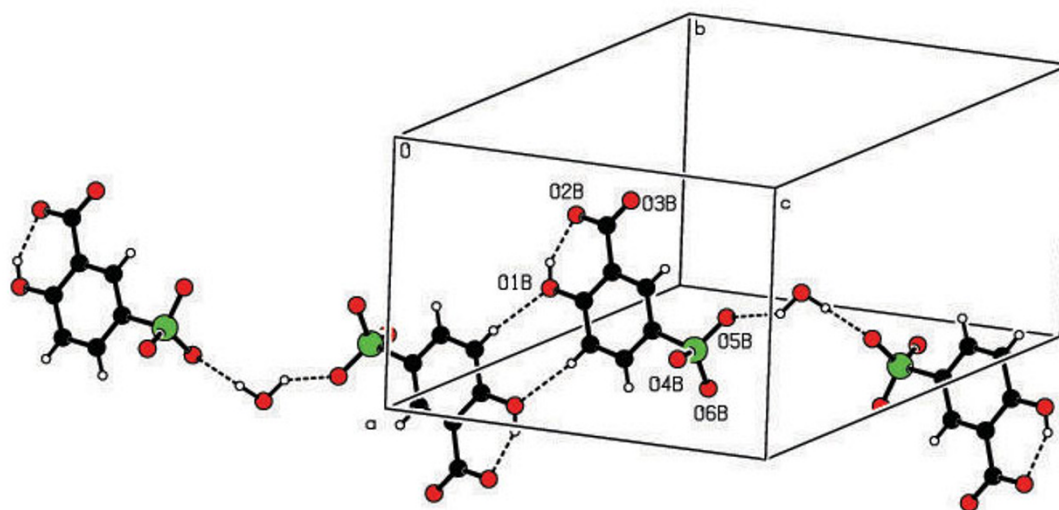
X-ray diffraction data were collected on a Bruker Nonius Kappa CCD area detector diffractometer by using MoK $\alpha$

( $\lambda$  0.71073 Å) for compounds 1 and 2 at 120(2)K. The structures were solved by direct methods and refined by full-matrix least squares (on  $F^2$ ) SHELXS97 and SHELXL97 [34], with the graphics produced using PLATON97 [35]. All the non-hydrogen atoms were located from a Fourier map and refined anisotropically. All the hydrogen atoms for compounds 1 and 2 were positioned geometrically and refined as riding. In compound 1, the O1 W of water is disordered and the hydrogen atoms are not found. In compound 2, the water (O1 W) hydrogen atoms are located from difference Fourier map. The O2 W of water is disordered, the hydrogen atoms are not found. The crystal data and details of structural determination for the compounds 1 and 2 are given in Table 2. CCDC reference numbers: 611485 and 611479. All CIF information can be found in Additional file 1.

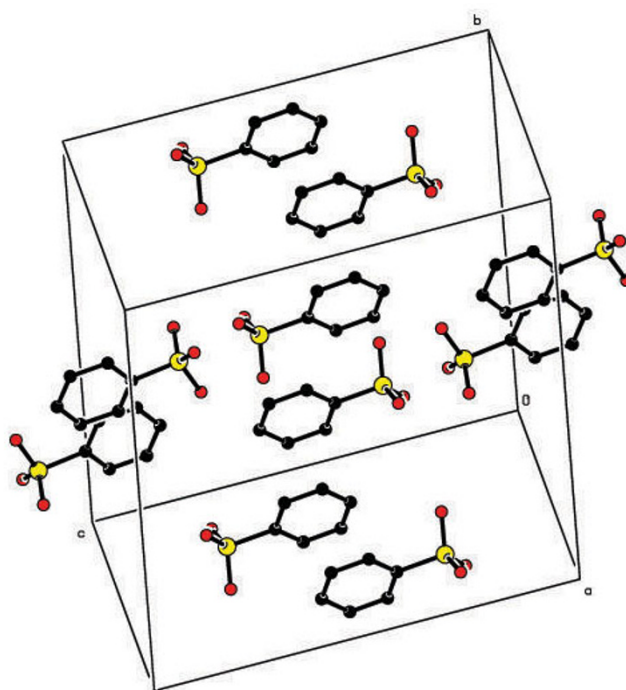




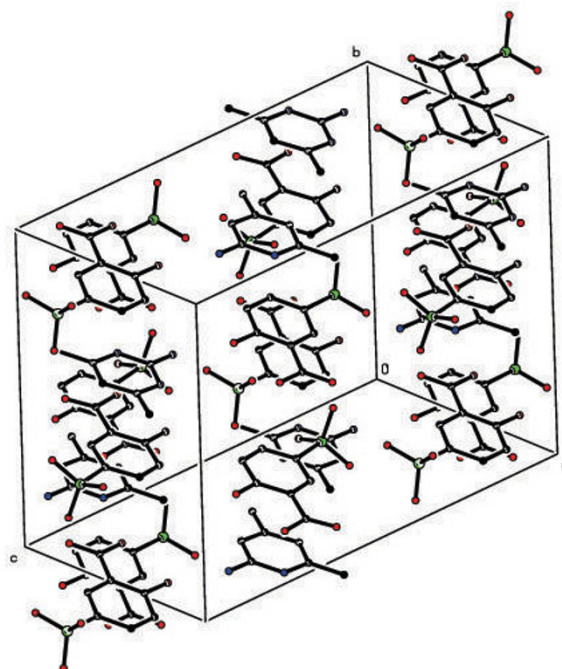
**Figure 6**  
One dimensional chain made up of sulfosalicylate and AMPY molecule in compound 2.



**Figure 7**  
A view of the supramolecular chain made up of sulfosalicylate and water molecule in compound 2.



**Figure 8**  
A view of  $\pi$ - $\pi$  stacking interaction between benzenesulfonate anions in compound 1.



**Figure 9**  
 $\pi$ - $\pi$  stacking interactions in compound 2.



Table 2: Crystallographic parameters for 1 and 2

| Properties                             | 1  | 2  |
|--|--|--|
| Formula                                | 2(C <sub>12</sub> H <sub>14</sub> Cl N <sub>4</sub> ),<br>2(C <sub>6</sub> H <sub>5</sub> O <sub>3</sub> S), O0.41 | 4(C <sub>6</sub> H <sub>10</sub> N <sub>3</sub> ),<br>2(C <sub>7</sub> H <sub>4</sub> O <sub>6</sub> S), H <sub>2</sub> O, O |
| M.wt                                   | 820.34   | 963.04   |
| Crystal System                         | Triclinic  | Triclinic  |
| Space group                            | P-1  | P-1  |
| a/Å°                                   | 10.2783(3)   | 9.2466(2)  |
| b/Å°                                   | 13.6919(3)   | 14.0976(3)   |
| c/Å°                                   | 15.4164(4)   | 17.6365(4)   |
| α/°                                    | 102.863(2)   | 94.0280(10)  |
| β/°                                    | 102.187(2)   | 101.1930(10)   |
| γ/°                                    | 108.805(2)   | 91.9680(10)  |
| V/Å <sup>3</sup>                       | 1905.83(10)  | 2247.00(9)   |
| Z                                      | 2  | 2  |
| Radiation λ/Å°                         | 0.71073  | 0.71073  |
| Dc/g cm <sup>-3</sup>                  | 1.429  | 1.423  |
| T/K                                    | 293(2)   | 293(2)   |
| μ/mm <sup>-1</sup>                     | 0.338  | 0.198  |
| F(000)                                 | 855  | 1012   |
| Reflection collected                   | 8768   | 10346  |
| Observed data [ $I > 2\sigma(I)$ ]     | 5759   | 8165   |
| Parameters refined                     | 498  | 606  |
| Final R <sub>1</sub> on observed data  | 0.0509   | 0.0605   |
| Final wR <sub>2</sub> on observed data | 0.1314   | 0.1555   |
| Structure solution                     | SHELXS97 [36]  | SHELXS97   |
| Structure refinement                   | SHELXL97   | SHELXL97   |
| Graphics                               | PLATON97 [37]  | PLATON97   |

### Authors' contributions

This work was prepared in the research group of PTM. He proposed the work and drafted the manuscript. KB participated in the design and presiding the experiments and drafted the manuscript. DEL collected the X-ray data and drafted the manuscript.

### Additional material

#### Additional file 1

Crystallographic Information. Contains all relevant CIF information.

Click here for file

[<http://www.biomedcentral.com/content/supplementary/1752-153X-1-28-S1.cif>]

### Acknowledgements

DL thanks the EPSRC National Crystallography Service (Southampton, England) for the X-ray data collection.

### References

- Desiraju GR: **Supramolecular synthons in Crystal engineering -A new organic synthesis.** *Angew Chem Int Ed Engl* 1995, **34**:2311-2327.
- Onoda A, Yamada Y, Doi M, Okamura TA, Ueyama N: **Dinuclear Calcium complex with weakly N-H...O hydrogen bonded sulfonate ligands.** *Inorg Chem* 2001, **40**:516-521.
- Cai J, Chen CH, Liao CZ, Yao JH, Hu XP, Chen XM: **Variation in the coordination mode of arenedisulfonates to copper(II) synthesis and structural characterization of six copper(II) arenedisulfonate complexes.** *J Chem Soc Dalton Trans* 2001:1137-1142.
- Cai J, Chen CH, Feng XL, Liao CZ, Chen XM: **A novel supramolecular synthon for H-bonded coordination networks: synthones and structures of extended 2- dimensional cadmium(II) arenedisulfonates.** *J Chem Soc Dalton Trans* 2001:2370-2375.
- Raj SB, Muthiah PT, Bocelli G, Olla R: **Metal-binding modes in sulfoxines: supramolecular network in (8-hydroxyquinoline-5-sulfonato-N<sup>1</sup>, O<sup>8</sup>)sodium(I).** *Acta Crystallogr Sect E* 2002, **58**:m513-m516.
- Russell VA, Etter MC, Ward MD: **Layered Materials by Molecular Design: Structural Enforcement by Hydrogen Bonding in Guanidinium Alkane- and Arenesulfonates.** *J Am Chem Soc* 1994, **116**(5):1941-1952.
- Etter MC, Adson DA: **The use of cocrystallization as a method of studying hydrogen bond preferences of 2-aminopyrimidine.** *J Chem Soc Chem Commun* 1990:589-591.
- Etter MC, Adson DA, Britton D: **2-Aminopyrimidine-succinic acid (1/1) cocrystal.** *Acta Crystallogr Sect C* 1990, **46**:933-934.
- Haynes DA, Chisholm JA, Jones W, Motherwell WDS: **Supramolecular synthon competition in organic sulfonates: A CSD survey.** *Cryst Eng Comm* 2004, **6**(95):584-588.
- Schwalbe CH, Cody V: **Structural characteristics of small-molecule antifolate compounds.** *Crystallography Reviews* 2006, **4**:267-300.
- Muthiah PT, Francis S, Rychlewska U, Warzajtis B: **Crystal Engineering of analogous and homologous organic compounds: Hydrogen bonding patterns in trimethoprim hydrogen phthalate and trimethoprim hydrogen adipate.** *Beil J Org Chem* 2006, **2**:8.
- Sethuraman V, Stanley N, Muthiah PT, Sheldrick W, Winter M, Luger P, Weber M: **Isomorphism and Crystal Engineering: Organic ionic ladders formed by supramolecular motifs in pyrimethamine salts.** *Cryst Growth Des* 2003, **3**:823-828.
- Stanley N, Sethuraman V, Muthiah PT, Luger P, Weber M: **Crystal engineering of organic salts: Hydrogen-bonded supramo-**

- lecular motifs in pyrimethamine hydrogen glutarate and pyrimethamine formate.** *Cryst Growth Des* 2002, **2**:631-635.
14. Hemamalini M, Muthiah PT, Sridhar B, Rajaram RK: **Pyrimethaminium sulfosalicylate monohydrate.** *Acta Crystallogr Sect E* 2005, **61**:o1480-o1482.
  15. Stanley N, Muthiah PT, Geib SJ, Luger P, Weber M, Messerschmidt M: **The novel hydrogen bonding motifs and supramolecular patterns in 2,4- diaminopyrimidine-nitrobenzoate complexes.** *Tetrahedron* 2005, **61**:7201-7210.
  16. Raj SB, Sethuraman V, Francis S, Hemamalini M, Muthiah PT, Bocelli G, Cantoni A, Rychlewska U, Warzajtis B: **Supramolecular organisation via hydrogen bonding in trimethoprim sulfonate salts.** *Cryst Eng Comm* 2003, **5(15)**:70-76.
  17. Hemamalini M, Muthiah PT, Rychlewska U, Plutecka A: **Hydrogen-bonding patterns in 2-amino-4,6-dimethylpyrimidinium hydrogen sulfate.** *Acta Crystallogr Sect C* 2005, **61**:o95-o97.
  18. Balasubramani K, Muthiah PT, Sridhar B, Rajaram RK: **Hydrogen-bonding patterns in 2-amino-4,6-dimethylpyrimidine-cinnamic acid (1/2).** *Acta Crystallogr Sect E* 2005, **61**:o4203-o4205.
  19. Balasubramani K, Muthiah PT, Lynch DE: **2-amino-4,6-dimethylpyrimidine-4- hydroxybenzoic acid (1/1).** *Acta Crystallogr Sect E* 2006, **62**:o2907-o2909.
  20. Olliaro P: **Mode of action and mechanisms of resistance for anti-malarial drugs.** *Pharmacol Ther* 2001, **89**:207-219.
  21. Hitchings GH, Burchall JJ: **Advances in Enzymology.** Volume 27. Edited by: Nord F. New York: Interscience; 1965:417.
  22. Tanaka R, Arai T, Hirayama N: **Structure of Pyrimethamine Hydrochloride.** *Analytical Sciences* 2004, **20**:175-176.
  23. Lynch DE, Singh M, Parsons S: **Molecular cocrystals of 2-amino-5- chlorobenzooxazole.** *Cryst Eng* 2000, **3**:71-79.
  24. Goswami SP, Ghosh K: **Molecular recognition: Chain length selectivity studies of dicarboxylic acids by the cavity of a new Troger's base receptor.** *Tetrahedron Lett* 1997, **38**:4503-4506.
  25. Goswami SP, Mahapatra AK, Ghosh K, Nigam GD, Chinnakali K, Fun HK: **2-aminopyrimidine-terephthalic acid (1:1) complex.** *Acta crystallogr Sect C* 1999, **55**:87-89.
  26. Sethuraman V, Muthiah PT: **Hydrogen bonded supramolecular ribbons in the antifolate drug pyrimethamine.** *Acta Crystallogr Sect E* 2002, **58**:o817-o818.
  27. Panneerselvam P, Muthiah PT, Francis S: **Co-existence of water-mediated and normal base pairs in a supramolecular ribbon in 2-amino-4,6- dimethylpyrimidinium bromide 2-amino-4,6-dimethylpyrimidine monohydrate.** *Acta Crystallogr Sect E* 2004, **60**:o747-o749.
  28. Sansom CE, Schwalbe CH, Lambert PA, Griffn PJ, Stevens MFG: **Structural studies on bio-active compounds. Part XV. Structure-activity relationships for pyrimethamine and a series of diaminopyrimidine analogues versus bacterial dihydrofolate reductase.** *Biochem Biophys Acta* 1989, **995**:21-27.
  29. De A, Basak AK, Roychowdhury P: **Crystallographic studies of an antineoplastic antifolate compound metoprine: [2,4-diamino-5-(3',4'-dichloro-phenyl)-6-methyl pyrimidine].** *Indian J Phys Sect A* 1989, **63**:553-563.
  30. Pirard B, Baudoux G, Durant F: **A database study of intermolecular NH...O hydrogen bonds for carboxylates, sulfonates and monohydrogen phosphonates.** *Acta Crystallogr Sect B* 1995, **51**:103-107.
  31. Etter MC: **Encoding and decoding hydrogen-bond patterns of organic compounds.** *Acc Chem Res* 1990, **23**:120-126.
  32. Bernstein J, Davis RE, Shimon L, Chang NL: **Patterns in Hydrogen Bonding: Functionality and Graph Set Analysis in Crystals.** *Angew Chem Int Ed Engl* 1995, **34**:1555-1573.
  33. Muthiah PT, Balasubramani K, Rychlewska U, Plutecka A: **Hydrogen-bonding and  $\pi$ - $\pi$  interactions in 2-amino-4,6-dimethylpyrimidinium salicylate.** *Acta Crystallogr Sect C* 2006, **62**:o605-o607.
  34. Hunter CA: **Meldola Lecture. The role of aromatic interactions in molecular recognition.** *Chem Soc Rev* 1994, **23**:101-109.
  35. Sheldrick GM: **SHELXL97: Programs for structure solution and refinement.** University of Göttingen, Germany; 1997.
  36. Spek AL: **PLATON97 Utrecht University, The Netherlands.** 1997.

Publish with **ChemistryCentral** and every scientist can read your work free of charge

"Open access provides opportunities to our colleagues in other parts of the globe, by allowing anyone to view the content free of charge."

W. Jeffery Hurst, The Hershey Company.

- available free of charge to the entire scientific community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:  
<http://www.chemistrycentral.com/manuscript/>



**ChemistryCentral**