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ORIGINAL PAPER

Efficient Syntheses, Crystal Structure and Thermal Properties of Gabapentin 4-Acetamido, 2-Mesitylene and 2,4-Dinitro Sulfonamides Derivatives

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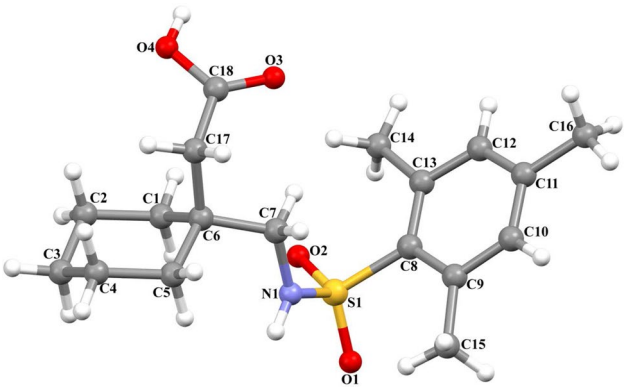
Abstract

Efficient syntheses of four derivatives G2–G5 of Gabapentin (G1) have been achieved. The structures of targeted compounds were investigated by elemental analysis, FT-IR, and ^{1}H-NMR spectroscopic method. Crystal structures of **G2** and **G4** determined by single crystal X-ray diffraction method are also described. In **G2** the molecules are stacked over each other in the form of layers and adjacent layers run parallel to each other. Intermolecular hydrogen bonding and van der Waals interactions are responsible for building the molecular assembly and packing of molecules in the unit. In **G4**, the molecules are arranged in parallel sheets formed by inter-molecular hydrogen bonds. The proposed synthetic route has high impact due to its simple reaction conditions of room temperature, water as a green solvent and short time to accomplish the reaction.

Graphical Abstract



Synthesis of Gabapentin sulfonamide derivatives and characterization by elemental analyzer, FT-IR, 1H-NMR, thermogravimetry and single crystal X-ray diffraction are described. The molecular structure of G4 showing the atom numbering scheme.

Keywords Gabapentin · Sulfonamides · Synthesis · Crystal structure · Thermal analysis

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Introduction

Gabapentin (Fig. 1) (1-(aminomethyl) cyclohexyl acetic acid is a generic drug marketed by Pfizer in 2004 [1]. It is an anti-convulsant medication, developed for the treatment of spasticity, partial epilepsy and also effective in a number of different animal seizure models [2–5]. This drug has also been used successfully for treating a range of neuropathic pain conditions, including post herpetic neuralgia [6],

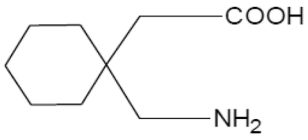


Fig. 1 Structure of Gabapentin **(G1)**

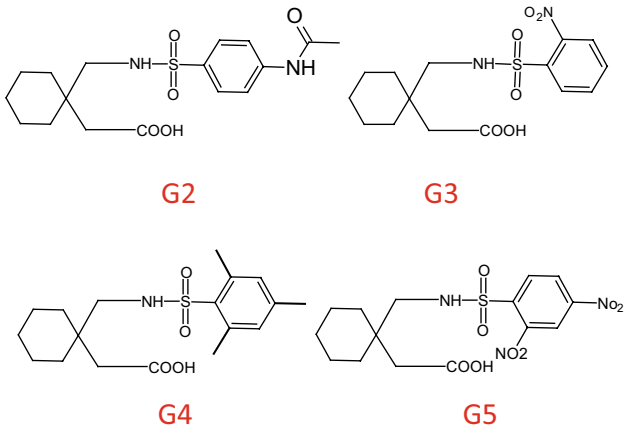


Fig. 2 Chemical Structures of **G2–G5**

diabetic neuropathy [7], trigeminal neuralgia, migraine and pain associated with cancer and multiple sclerosis [8–11]. The binding sites of Gabapentin are located on neurons in brain areas which are rich in glutaminergic synapses. It is a strong competitive inhibitor of brain branched chain amino acid aminotransferase enzyme, involved in the glutamate synthetic pathway [12]. Gabapentin inhibits voltage-dependent Ca^{2+} channel currents recorded from cortical neurons [13–16].

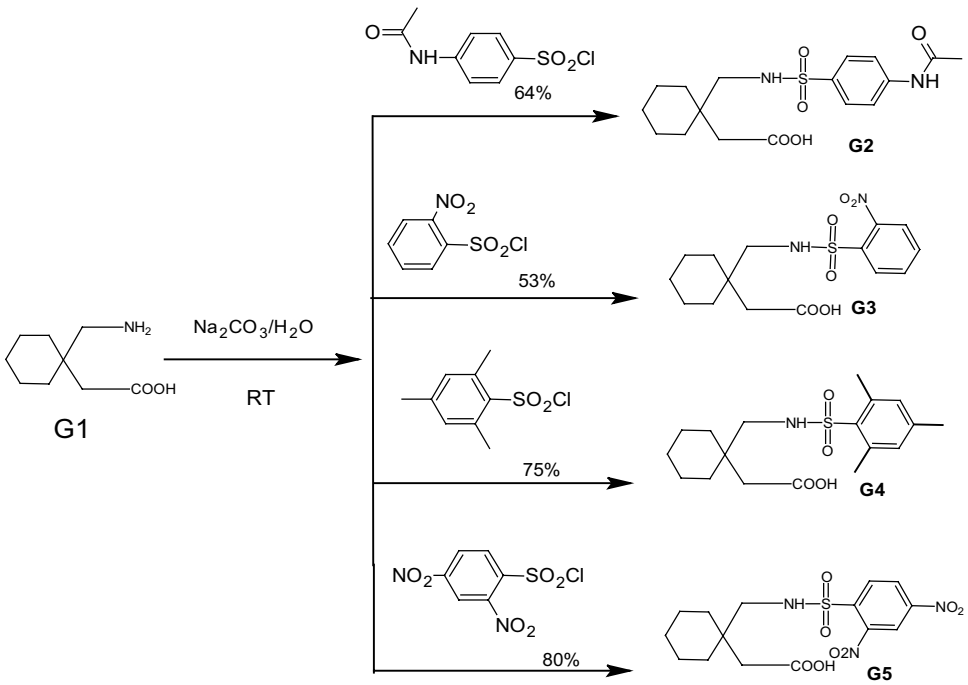
Due to stability and tolerance in human beings sulfonamide derivatives are well known pharmaceutical agents since this group has been the main functional part of the most of the drug structures [17]. Sulfonamide derivatives are used in meningitis, urinary tract infections, streptococcal pharyngitis, bacillary dysentery, trachoma, nocardiasis and conjunctivitis [18–20]. Such derivatives of sulfonamides attracted attention and keeping in view of their pharmaceutical importance, herein, in this research article, synthesis, crystal structure and thermal properties of {1-[({[4(acetylamino)phenyl]sulfonyl}amino)methyl] cyclohexyl} acetic acid **(G2)**, 2-{1-[(2-Nitrobenzenesulfonamido)-methyl] cyclohexyl} acetic acid **(G3)**, 2-[(2,4,6-Trimethylphenyl) sulfonyl] amino} methyl) cyclohexyl] acetic acid **(G4)** and [2,4-Dinitrophenyl)]-sulfonyl] amino} methyl) cyclohexyl] acetic acid **(G5)** have been reported (Fig. 2). In the current study we have reported open chain sulfonamides as summarized in Scheme 1, while cyclization/lactimization of Gabapentin which will be described elsewhere.

Experimental

Materials and Methods

All chemicals and materials used in this study were of analytical grade. 4-acetamidobenzenesulfonyl chloride, 2-nitrobenzenesulfonyl chloride, 2-naphthalene sulfonyl

Scheme 1 Synthesis of Gabapentin sulfonamides derivatives



chloride, 2-Mesitylene sulfonyl chloride, 2,4-dinitro benzene sulfonyl chloride were purchased from Alfa Aesar (26 Partridge Rd, Ward Hill, MA, 01835 USA). Sodium hydride was obtained from Sigma Aldrich (Germany). Methanol, ethyl acetate and dimethyl formamide were obtained from Panreac (Spain). Analytical grade HCl was purchased from Merck. Solvents were purified through distillation wherever necessary.

Working standard of gabapentin was kindly provided by Lahore Pharmaceuticals, Lahore, Pakistan and characterized for assay before use. All melting points were obtained on an Electro thermal (Griffin 1090) melting point apparatus and are reported here without correction. The IR spectra of the compound were scanned through Perkin Elmer 1600 FT-IR (USA) and MIDAC- M 2000 (USA) by using KBr pellets over the range 4000–400 cm^{-1}. Elemental analysis (CHNS) was performed by using Vario Micro Cube, Elementar, Germany. Mass spectra were recorded on a JEOL MS Route with Ionization mode: $EI^{+\cdot}$ ^{1}H-NMR spectra were recorded on Bruker AVANCE AV 600 and DPXQ 400 spectrometers. The single-crystals data were collected using a Bruker Kappa APEX II CCD diffractometer (graphite monochromated Mo-Kα radiation, $\lambda = 0.71073$ Å) at room temperature and data reductions were performed using SAINT [21]. The structures were solved by direct methods with SHELXS and the resulting atomic models were developed and refined against $|F|^2$ using SHELXL [22]. The "observed data" threshold for calculating the $R(F)$ residuals was set as $I > 2\sigma(I)$. The C and N bound H atoms were placed in idealised locations (C–H = 0.96–0.97 Å, N–H = 0.86 Å) and refined as riding atoms. In G4, in spite of the relatively low errors and accurate location of the non-H atoms, the low quality of the crystal did not allow the refinement of anisotropic parameters for one oxygen atom (O3). The O-bound H atoms were located in the difference Fourier maps and refined as riding on their relative atoms. All non-hydrogen atoms were refined with anisotropic parameters. The structural models were analysed and validated with PLATON [23] and full refinement details are given in the CIF (Crystal Information File). Program used for molecular graphics was Mercury [24]; software used to prepare material for publication was WinGX [25] and PLATON [23].

Synthesis

{1-[({[4(Acetylamino)phenyl]sulfonyl}amino)methyl] Cyclohexyl} Acetic Acid (G2)

To a solution of Gabapentin (0.171 g, 1.00 mmol) and water (10 mL), 1 M sodium carbonate was added to adjust the pH 8. Then added 4-acetamidobenzenesulfonyl chloride (0.233 g, 1.00 mmol) and the mixture was stirred at room temperature keeping the pH of the mixture up to 8.0 by using sodium carbonate solution. Progress and completion of the reaction was confirmed by TLC. After 3 h, the pH of mixture was adjusted to 2.0 by 1 M HCl. White precipitates were produced, filtered and washed with distilled water. Colorless crystals were obtained after recrystallization from methanol. Yield 64%, m.p. 182 °C. ^{1}H NMR (600 MHz, CD_3OD, δ, ppm, *J*/Hz): 7.76 (d, J = 8.4, 2H, H-2′, H-6′), 7.74 (d, J = 8.4, 2H, H-3′, H-5′), 2.88 (s, 2H, H-9), 2.29 (s, 2H, H-2), 2.14 (s, 3H, H-1″), 1.43–1.39 (m, 10H, H-7-H-3). IR ν_{max} (KBr, cm^{-1}) 1155 {symm $(S=O)_2$ stretch}, 1322, 1403 (C–N stretching), 1690, (C=O), 1594 (C–C aromatic ring stretch), 3250 (amide NH), 3338 (sec sulfonamide). Anal. Calcd. For $C_{17}H_{24}N_2O_5S$ (368.447): C, 55.42; H, 6.57; N, 7.60, S, 8.70. Found: C, 55.05; H, 6.96; N, 7.52; S, 8.978%. MS m/z (%): 304 ($M^+ - SO_2$), 286 (100), 244 (91), 227 (20), 197 (43), 120 (32), 107 (17), 92 (22), 81 (37), 65 (17), 43 (20).

2-{1-[(2-Nitrobenzenesulfonamido)-Methyl] Cyclohexyl} Acetic Acid (G3)

The procedure was same as described for G2 except that 4-acetamidobenzenesulfonyl chloride was replaced by 2-nitrobenzenesulfonyl chloride (0.221 g, 1.00 mmol). Yield 53%, m.p. 141 °C. ^{1}H NMR (600 MHz, CD_3OD, δ, ppm, *J*/Hz): 8.07 (dd, *J* = 2.6, 8.0, 1H, H-3′), 7.86 (dd, *J* = 2.6, 8.0, 1H, H-6′), 7.80 (dd, *J* = 2.6, 6.0, 2H, H-4′, H-5′), 3.07 (s, 2H, H-9), 2.31 (s, 2H, H-2), 1.47–1.41 (m, 10H, H-3-H-7). IR ν_{max} (KBr, cm^{-1}) 1167 {symm $(S=O)_2$ stretch}, 1358 (N O aromatic ring), 1415 (C–N stretching), 1694 (C=O), 1540 (C–C aromatic ring stretch), 2930 (C–H Stretching) 3100 (amide NH), 3346 (sec sulfonamide). Anal. Calcd. For $C_{15}H_{20}N_2O_6S$ (356.394) C, 50.55; H, 5.66; N, 7.86, S, 9.00. Found: C, 50.56; H, 5.39; N, 8.06; S,8.64%. MS m/z (%): 292 ($M^+ - SO_2$), 228(100), 186(32), 182 (13), 152 (20), 95 (34), 81 (35), 67 (18), 55(10), 44(8.8), 41(9).

2-[2,4,6-Trimethylphenyl) Sulfonyl] Amino} Methyl) Cyclohexyl] Acetic Acid (G4)

The procedure was same as described for G2 except that 4-acetamidobenzenesulfonyl chloride was replaced by 2-Mesitylene sulfonyl chloride (0.256 g, 1.169 mmol). Yield 75%, m.p. 138–140 °C). ^{1}H-NMR (600 MHz, CD_3OD, δ, ppm, *J*/Hz):, δ 6.93(s, 2H, H-3′, H-5′), 2.79 (s, 2H, H-9), 2.62 (s, 6H, H-1″), 2.33 (s, 3H, H-2″), 2.27 (s, 2H, H-2), 1.38–1.36 (m, 10H, H-3-H-7). IR ν_{max} (KBr, cm^{-1}) 3280 (sec sulfonamide), 2975, 2936 (CH stretching), 1652 (C H bending), 1542 (C–C aromatic ring stretch), 1384 (asymm $(S=O)_2$ stretch), 1169 {symm $(S=O)_2$ stretch}, 1130 (aromatic C–Cl), 549 (out-of-plane aromatic ring C–C bend). Analytical calcd. For $C_{18}H_{27}NO_4S$ (353.476): C, 61.16; H, 7.70; N, 3.96; S, 9.053%. Found C, 60.86, H, 7.69, N, 4.07,

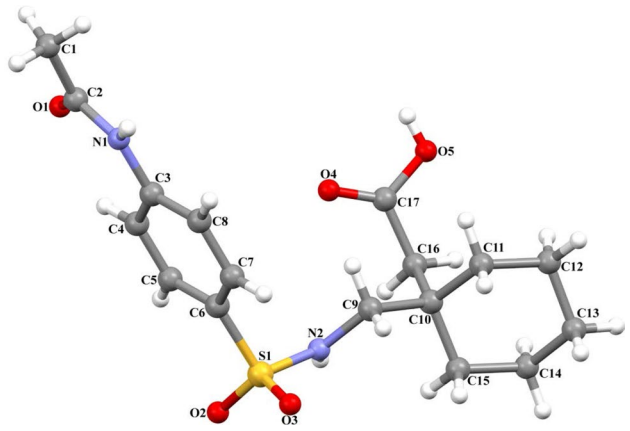


Fig. 3 The molecular structure of **G2** showing the atom numbering scheme

S, 8.99%. MS m/z (%): (353.2 M^+), 289 (3) 271 (13), 183 (55), 119 (100), 95 (21), 91 (60), 77 (75), 67 (34), 55 (36).

[(2,4-Dinitrophenyl)]-Sulfonyl] Amino} Methyl) Cyclohexyl] Acetic Acid (G5)

The procedure was same as described for G2 except that 4-acetamidobenzenesulfonyl chloride was replaced by 2,4-dinitro benzene sulfonyl chloride (0.312 g, 1.169 mmol). Yield 80%, m.p 142. ^{1}H NMR (600 MHz, CD_3OD, δ, ppm, *J*/Hz): 8.72 (d, $J = 1.8$, 1H, H-3′), 8.60 (dd, $J = 1.8$, 8.4, 1H, H-5′), 8.32 (d, $J = 8.4$, 1H, H-6′), 3.14 (s, 2H, H-9), 2.31 (s, 2H, H-2), 1.48–1.40 (m, 10H, H-3-H-7). IR ν_{max} (KBr, cm^{-1}) 3250 cm^{-1} (sec sulfonamide), 3072 cm^{-1} (C–H stretching), 2925, 2853 (C=O stretching cyclic), 1505 cm^{-1} (C=C aromatic ring stretch), 1363 cm^{-1} {asymm (S=O) 2 stretch} and 1171 cm^{-1} {symm (S=O) 2 stretch}, 767 cm^{-1} (in-phase –CH– out-of-plane bending vibration or in-phase –CH– wagging). Anal. Calcd. For ($C_{15}H_{19}N_3O_8S$) (401.392), C, 44.88, H, 4.77, N, 10.47, S, 7.99% Found. C, 44.76, H, 4.85, N, 10.58, S, 8.17%. MS m/z (%): 337(M^+-SO_2), 309 (3), 290 (20), 249(19), 228 (100), 185 (48), 181 (34), 154 (23), 152 (39), 123 (20), 109 (13), 95 (49), 91 (34),80 (23), 79 (20), 67 (36), 55 (28), 43 (40), 41 (27).

Results and Discussion

Crystallographic Studies

Crystallographic Description of G2

The molecular structure of G2 with the atom numbering scheme, is shown in Fig. 3. Details of crystal structure, selected bond distances and angles are described in Tables 1 and 2 respectively. The cyclohexane ring is present in chair conformation with φ = 333°, θ = 178.5° and Q = 0.553 Å as

Table 1 Parameters for data collection and structure refinement of G2 and G4

	G2	G4
Chemical formula	$C_{17}H_{24}N_2O_5S$	$C_{18}H_{27}NO_4S$
M_r	368.44	353.47
Cell setting	Monoclinic	Triclinic
Space group	$P2_1/c$	P − 1
Temperature (K)	296	
a, b, c (Å)	16.3533 (9)	8.003 (5)
	13.4604 (6)	11.178 (5)
	8.6325 (4)	11.291 (5)
α (°)	90.000 (5)°	68.381 (5)°
β (°)	98.264 (2)°	79.069 (5)°
γ (°)	90.000 (5)°	85.427 (5)°
V (Å^3)	1880.47 (16)	921.9 (8)
Z	4	2
D_x (g/cm^{-3})	1.301	1.273
μ (mm^{-1})	0.221	0.196
Crystal size (mm)	0.21 × 0.11 × 0.11	0.34 × 0.31 × 0.26
No. of measured, independent and observed reflections	11,604, 3692, 2460	44,494, 4782, 3081
Data collection range (°)	2.0–26.0	2.0–28.9
R[$F^2 > 2\sigma(F^2)$], wR(F^2) Goodness-of -fit	0.0534, 0.148, 1.02	0.659, 0.2701, 1.017
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.35, − 0.39	0.38, − 0.39

puckering parameters and forms an angle of 109.51(7)° and 109.40(3)° with C9–C10 and C10–C16 bonds respectively. The torsion angle of N1–C3–C4–C5 and C9–N2–S1–C6 are − 177.6(3)° and 64.3(2)° respectively. The interplaner distance between two molecules is 7.105(5) Å as calculated on the basis of phenyl rings of each molecule. The molecules are stacked over each other in the form of layers and adjacent layers run parallel to each other. Molecules of G2 are linked into sheets by a combination of O–H···O and N–H···O hydrogen bonds (Table 3). N1 atom acts as hydrogen-bond donor, via atom H1, to atom O2 in the molecule at (− x, 1/2 + y, 1/2−z), forming a C(8) chain running which is parallel to the [010] direction (Fig. 4a). N2 atom acts as hydrogen-bond donor, via atom H2, to atom O1 in the molecule at (− x, − y, − z), forming a centrosymmetric $R_2^2(20)$ ring centered at (0, 0, 0). O5 atom acts as hydrogen-bond donor, via atom H5A, to atom O3 in the molecule at (x, y, − 1 + z),forming a C(9) chain running which is parallel to the [001] direction. The combination of these hydrogen bonds produce $R_4^4(34)$ rings which are running parallel to the [001] direction (Fig. 4b).

Table 2 Selected bond lengths (Å) and bond angles (°) for **G2** and **G4**

	Bond	Length (Å)	Angle	(°)
G2	C6–S1	1.752 (3)	O2–S1–O3	118.6 (1)
	C1–C2	1.500 (4)	O2–S1–N2	106.9 (1)
	C2–N1	1.352 (3)	N2–S1–C6	107.6 (1)
	N2–S1	1.609 (2)	C9–C10–C16	111.4 (2)
	O2–S1	1.4307 (9)	O15–C10–C16	109.4 (2)
G4	S1–O2	1.419 (2)	O2–S1–O1	117.2 (1)
	S1–N1	1.612 (2)	O1–S1–C7	110.1 (1)
	S1–C7	1.778 (2)	N1–S1–C7	105.9 (1)
	C11–C17	1.546 (3)	C6–C7–S1	117.3 (2)
	O4–C18	1.305 (3)	N1–C10–C11	114.3 (2)

Table 3 Hydrogen-bond parameters (Å, °) of Compound **G2** and **G4**

D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
G2				
O5–H5^{i} ···O3	0.820	1.989	2.806	173.74 (2)
N1–H1^{ii} ···O2	0.860	2.061	2.921	177.88 (3)
N2–H2^{iii} ···O1	0.860	2.245	2.950	139.13 (2)
G4				
N1–H1 ···O1^{i}	0.860	2.177	2.975	154.25
O4–H4··· O3^{ii}	0.820	1.846	2.664	174.85

Symmetry codes: (i) x, y, − 1 + z (ii) − x, 1/2 + y, 1/2−z (iii) − x, − y, − z for **G2**; (i) − x + 2, − y, -z + 2 (ii) −x + 1, −y + 1, −z + 1 for **G4**.

Crystallographic Description of G4

The molecular structure of G4 with the atom labeling is shown in Fig. 5. Details of crystal structure, selected bond distances and angles are described in Tables 1 and 2 respectively. The cyclohexane ring exhibits a chair conformation with φ = 111°, θ = 2.9° and Q = 0.551 Å as puckering parameters and forms an angle of 109.35(9)° with C6–C7 bond. The mean plane of mesitylene ring is approximately planar.

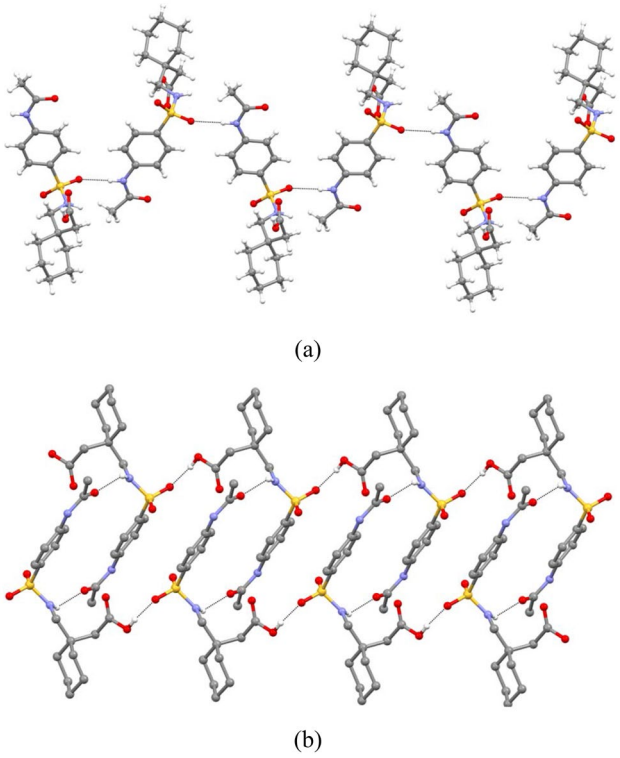


Fig. 4 The formation of C(8) chain (**a**) and $R_2^2(20)R_4^4(34)$ rings (**b**) in **G2**

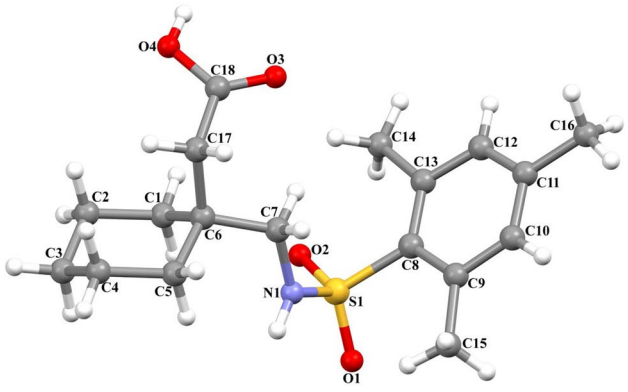


Fig. 5 The molecular structure of **G4** showing the atom numbering scheme

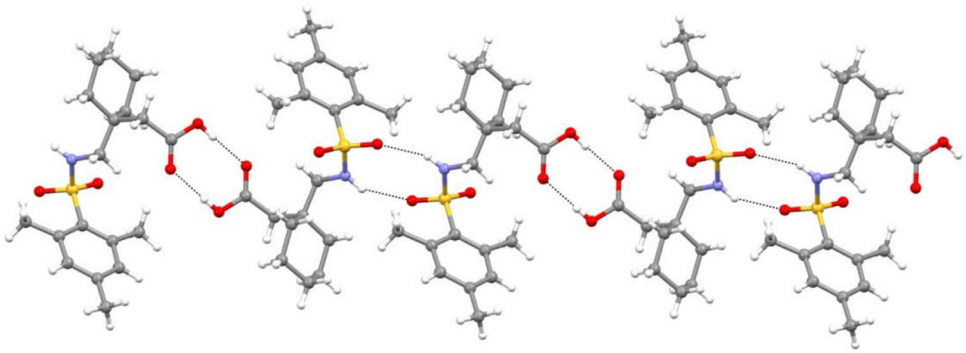


Fig. 6 The formation of edge-fused$R_2^2(8)$ rings in **G4**

The torsional angles for C8–S1–N1–C7 and C6–C7–N1–S1 are 52.08(2)° and125.55(3)°, respectively. Molecules of G4 are linked into sheets by a combination of O–H···O and N–H···O hydrogen bonds (Table 3). N1 atom acts as hydrogen-bond donor, via atom H1, to atom O1 in the molecule at (−x+2, −y, −z+2), forming a centrosymmetric$R_2^2(8)$ ring centered at (1, 0, 1). Similarly, atom O4 atom acts as hydrogen-bond donor, via atom H4, to atom O3 in the molecule at (−x+1, −y+1, −z+1), forming a centrosymmetric$R_2^2(8)$ ring centered at (1/2, 1/2, 1/2). The combination of these hydrogen bonds produce edge-fused $R_2^2(8)$ rings which are running parallel to the [111] direction (Fig. 6).

Thermogravimetric Analysis

Thermal Analysis of G2 and G3

The results of thermal analysis of the compound **G2** is depicted in Fig. 7. Compound is thermally stable up to 175 °C and afterwards it melts around 195 °C and starts decomposing between 200 and 275 °C which is followed by rapid decomposition process completed near 395 °C. Total weight loss of 98% due to successive release of organic compounds by evaporation process.

The decomposition pattern of the **G3** is illustrated in Fig. 8. A principle sharp endothermic peak was observed around 152 °C attributed to the melting of compound. Compound is thermally stable and starts decomposing, followed by sudden decomposition up to 250–335 °C. Total weight loss of 97% due to successive release of organic compounds by evaporation process.

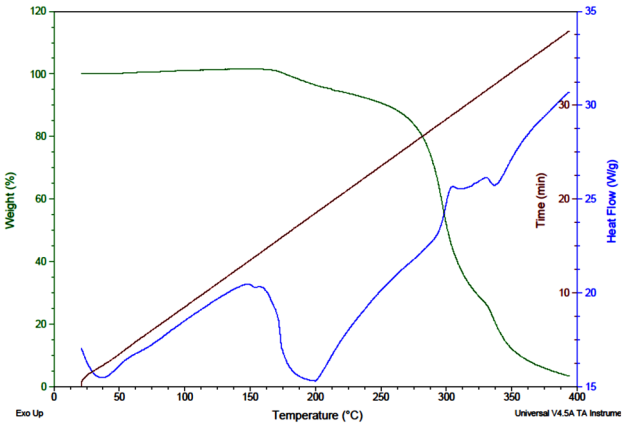


Fig. 7 TGA/DSC Curve of **G2**

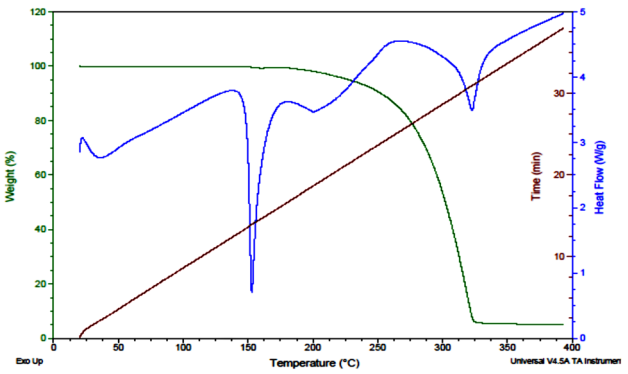


Fig. 8 TGA/DSC Curve of **G3**

Conclusion

Novel Gabapentin open chain derivatives have been isolated by one step reaction using water as a solvent at room temperature. This research work is an effort to momentously augment the synthesis of different derivatives of Gabapentin by substitution of sulfonamide functional groups. In G2 N1, via atom H1, to atom O1 in the molecule are responsible to generate centrosymmetric$R_2^2(8)$ ring centered at (1, 0, 1) while in G4 N2 atom, via atom H2, to atom O1 form a centrosymmetric $R_2^2(20)$ ring centered at (0, 0, 0). These derivatives can be used to discover their potential applications in antiepileptic, anti-viral, anti-cancer, anti-microbial and anti-inflammatory drugs.

Supplementary Material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 874496 for G2 and 933707 for G4. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk). Compound G3 (Doi:10.1107/S1600536810012699) has been published in Acta Crystallographica Section *E* and their single crystal and refinement parameters can be obtained by using DOI number.

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