

**Improved, selective, human intestinal carboxylesterase inhibitors designed to modulate 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (irinotecan; CPT-11) toxicity**

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Physical properties of the sulfonamides synthesized for this article.

Compound	MP (°C)	<sup>1</sup> H NMR (400MHz, DMSO d <sub>6</sub> )	<sup>13</sup> C NMR (400MHz, DMSO d <sub>6</sub> or acetone d <sub>6</sub> )	HRMS ESI [M <sup>+</sup> ]	Elemental Analysis
<b>14</b> White solid	225-227 (dec)	δ 10.4 (s, 2H, NH x 2), δ 7.7 (m, J = 7.68 Hz, 4H), δ 7.5 (m, J = 7.33 Hz, 4H), δ 6.94 (s, 4H)	δ 159.23, 156.69, 135.83, 133.40, 130.28, 126.74, 124.81, 121.30, 117.18, 116.98	424.4	Anal. (C <sub>18</sub> H <sub>14</sub> F <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 50.94, H 3.32, F 8.95, N 6.60, O 15.08, S 15.11; found, (%) C 50.93, H 3.37, F 8.92, N 6.61, O 15.19, S 15.25
<b>15</b> White solid	228-230 (dec)	δ 10.25 (s, 2H, NH X 2), δ 7.58 (m, J = 7.3 Hz, 2H), δ 7.48 (m, J = 7.0 Hz, 4H), δ 7.43 (d, J = 2H); δ 6.98 (s, 4H);	δ 162.69, 160.22, 141.16, 133.77, 131.54, 122.80, 121.93, 120.13, 113.63, 113.39	424.4	Anal. (C <sub>18</sub> H <sub>14</sub> F <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 50.94, H 3.32, F 8.95, N 6.60, O 15.08, S 15.11; found, (%) C 51.08, H 3.32, F 8.68, N 6.65, O 15.25, S 15.30
<b>16</b> White solid	250-252 (dec)	δ 10.16 (s, 2H, NH x 2), δ 7.8 (s, J = 7.71 Hz, 4H), δ 7.5 (m, J = 7.36 Hz, 4H), δ 7.0 (m, J = 6.92 Hz, 4H)	δ 165.34, 163.24, 135.49, 133.88, 129.60, 121.79, 116.38	424.4	Anal. (C <sub>18</sub> H <sub>14</sub> F <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 50.94, H 3.32, F 8.95, N 6.60, O 15.08, S 15.11; found, (%) C 50.79, H 3.34, F 8.78, N 6.61, O 15.33, S 14.87
<b>17</b> Pale pink solid	220-222 (dec)	δ 10.3 (s, 2H, NH x 2), δ 7.75 (m, J = 7.43 Hz, 4H), δ 7.55 (m, J = 7.45 Hz, 4H), δ 7.0 (s, 4H);	δ 136.22, 133.75, 124.56, 122.07	457.4	Anal. (C <sub>18</sub> H <sub>14</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 47.27, H 3.09, Cl 15.50, N 6.13, O 13.99, S 14.02; found, (%) C 47.15, H 3.11, Cl 15.72, N 6.09, O 13.78, S 14.07
<b>18</b> White solid	243-245 (dec)	δ 10.2 (s, 2H, NH x 2), δ 7.9 (m, J = 7.82 Hz, 4H), δ 7.7 (dd, J = 7.62 Hz, 2H), δ 7.5 (t, J = 7.48, 2H) δ 7.0 (s, 4H)	δ 141.07, 135.69, 133.76, 131.34, 128.85, 125.54, 121.97	546.2	Anal. (C <sub>18</sub> H <sub>14</sub> Br <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 39.58, H 2.55, Br 26.96, N 5.13, O 11.72, S 11.74; found, (%) C 39.22, H 2.53, Br 26.94, N 4.88, O 11.54, S 11.43
<b>19</b> White solid	287-289 (dec)	δ 10.2 (s, 2H, NH x 2), δ 7.73 (d, J = 13.8 Hz, 4H), δ 7.55 (d, J = 13 Hz, 4H), δ 6.95 (s, 4H)	δ 138.39, 133.79, 132.16, 128.53, 126.66, 115.25	546.2	Anal. (C <sub>18</sub> H <sub>14</sub> Br <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 39.58, H 2.55, Br 29.26, N 5.13, O 11.72, S 11.74; found, (%) C 39.25, H 2.55, Br 28.94, N 4.86, O 11.58, S 11.47
<b>20</b> White solid	253-255 (dec)	δ 10.2 (s, 2H, NH X 2), δ 7.7 (m, J = 7.68 Hz, 2H), δ 7.25 (m, J = 7.19 Hz, 4H), δ 7.0 (s, 4H)	δ 160.01, 159.98, 136.03, 135.81, 121.21, 116.23, 113.38	460.4	Anal. (C <sub>18</sub> H <sub>12</sub> F <sub>4</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 46.96, H 2.63, F 16.51, N 6.08, O 13.90, S 13.93; found, (%) C 46.72, H 2.79, F, N 6.61, O 13.95, S 13.83
<b>21</b> Pink solid	238-240 (dec)	δ 10.26 (s, 2H, NH x 2), δ 7.55 (m, J = 7.64 Hz, 6H), δ 7.0 (s, 4H)	δ 140.94, 133.76, 132.82, 131.15, 126.07, 125.22, 121.97	460.4	Anal. (C <sub>18</sub> H <sub>12</sub> F <sub>4</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 46.96, H 2.63, F 16.51, N 6.08, O 13.90, S 13.93; found, (%) C 46.72, H 2.78, F 16.23, N 6.21, O 13.94, S 13.83

<b>22</b> Pale pink solid	234-236	$\delta$ 10.5 (s, 2H, NH x 2), $\delta$ 7.85 (m, J = 7.6 Hz, 4H), $\delta$ 7.60 (d, J = 7.5 Hz, 2H), $\delta$ 7.0 (s, 4H);	$\delta$ 163.33, 160.83, 142.36, 133.71, 122.28, 110.30, 108.78	460.4	Anal. (C <sub>18</sub> H <sub>12</sub> F <sub>4</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 46.96, H 2.63, F 16.51, N 6.08, O 13.90, S 13.93; found, (%) C 46.61, H 2.78, F 16.35, N 6.03, O 13.96, S 13.86
<b>23</b> White solid	243-245	$\delta$ 10.5 (s, 2H, NH x 2), $\delta$ 8.0 (dd, J = 7.59 Hz, 4H), $\delta$ 7.2 (d, J = 7.0 Hz, 4H);	$\delta$ 133.64, 121.39, 112.22	496.4	Anal. (C <sub>18</sub> H <sub>10</sub> F <sub>6</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 43.55, H 2.03, F 22.96, N 5.64, O 12.89, S 12.92; found, (%) C 43.39, H 2.03, F 22.95, N 5.52, O 13.13, S 12.96
<b>24</b> Pink solid	296-298 (dec)	$\delta$ 10.5 (2, 2H, NH x 2), $\delta$ 7.95 (d, J = 13.4, 4H), $\delta$ 7.75 (d, J = 13.4 Hz, 2H), $\delta$ 7.0 (s, 4H)	$\delta$ 138.42, $\delta$ 134.86, $\delta$ 134.02, $\delta$ 133.01, $\delta$ 128.66, $\delta$ 128.38, $\delta$ 121.06	526.4	Anal. (C <sub>18</sub> H <sub>12</sub> Cl <sub>4</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 41.08, H 2.30, Cl 26.95, N 5.32, O 12.16, S 12.19; found, (%) C 40.74, H 2.41, Cl 27.04, N 5.47, O 12.12, S 11.85
<b>26</b> Pink solid	293-295 (dec)	$\delta$ 10.4 (s, 2H, NH x 2), $\delta$ 7.7 (m, J = 7.76 Hz, 4H), $\delta$ 7.66 (dd, J = 7.56 Hz, 2H), $\delta$ 7.0 (s, 4H)	$\delta$ 139.36, 135.96, 133.69, 132.01, 131.54, 126.62, 122.20	526.4	Anal. (C <sub>18</sub> H <sub>12</sub> Cl <sub>4</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 41.08, H 2.30, Cl 26.95, N 5.32, O 12.16, S 12.19; found, (%) C 41.17, H 2.25, Cl 27.02, N 5.31, O 12.12, S 12.12
<b>27</b> Pink solid	289-291 (dec)	$\delta$ 10.5 (s, 2H, NH x 2), $\delta$ 7.9 (s, 2H), $\delta$ 7.6 (s, 4H), $\delta$ 7.0 (s, 4H);	$\delta$ 142.07, 134.94, 133.64, 132.54, 125.03, 122.30	526.4	Anal. (C <sub>18</sub> H <sub>12</sub> Cl <sub>4</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 41.08, H 2.30, Cl 26.95, N 5.32, O 12.16, S 12.19; found, (%) C 41.19, H 2.35, Cl 27.0, N 5.32, O 12.02, S 12.24
<b>46</b> Yellow solid	243-245 (dec)	$\delta$ 9.8 (s, 2H, NH x 2), $\delta$ 7.7 (m, J = 7.68 Hz, 4H), $\delta$ 7.45 (t, J = 7.24 Hz, 4H), $\delta$ 1.76 (s, 12H);	$\delta$ 140.28, 137.29, 134.47, 131.94, 129.22, 128.38, 15.99	480.6	Anal. (C <sub>22</sub> H <sub>22</sub> F <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 54.99, H 4.61, F 7.91, N 5.83, O 13.35, S 13.35; found, (%) C 54.75, H 4.74, F 7.68, N 5.91, O 13.30, S 13.23
<b>47</b> Yellow solid	247-249 (dec)	$\delta$ 9.62 (s, 2H, NH x 2), $\delta$ 7.7 (d, J = 7.76 Hz, 2H), $\delta$ 7.55 (m, J = 7.67 Hz, 6H), $\delta$ 1.79 (s, 12H);	$\delta$ 143.14, 134.49, 133.67, 132.42, 1313.91, 131.27, 125.97, 125.03, 124.71, 15.92	513.4	Anal. (C <sub>22</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 51.46, H 4.32, Cl 13.81, N 5.46, O 12.46, S 12.49; found, (%) C 51.39, H 4.34, Cl 13.65, N 5.31, O 12.33, S 12.42
<b>48</b> Yellow solid	216-218 (dec)	$\delta$ 9.5 (s, 2H, NH x 2), $\delta$ 7.65 (s, 4H), $\delta$ 7.45 (s, 4H), $\delta$ 1.76 (s, 12H)	$\delta$ 140.29, 137.30, 134.49, 131.96, 129.22, 128.39, 128.22, 16.0	513.4	Anal. (C <sub>22</sub> H <sub>14</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 51.46, H 4.32, Cl 13.81, N 5.46, O 12.46, S 12.49; found, (%) C 51.62, H 4.23, Cl 13.53, N 5.36, O 12.36, S 12.26
<b>49</b> Yellow solid	241-243 (dec)	$\delta$ 9.62 (s, 2H, NH x 2), $\delta$ 7.9 (d, J = 7.88 Hz, 2H), $\delta$ 7.75 (d, J = 7.71 Hz, 2H), $\delta$ 7.65 (d, J = 7.63, 2H), $\delta$ 7.59 (m, J = 7.56, 2H) 1.79 (s, 12H)	$\delta$ 143.15, 134.51, 131.93, 131.27, 125.98, 128.03, 15.93	602.4	Anal. (C <sub>22</sub> H <sub>22</sub> Br <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 43.87, H 3.68, Br 26.53, N 4.65, O 10.62, S 10.65; found, (%) C 43.92, H 3.59, Br 26.46, N 4.72, O 10.62, S 10.42
<b>50</b> Yellow solid	295-297 (dec)	$\delta$ 9.62 (s, 2H, NH x 2), $\delta$ 7.9 (s, 8H), $\delta$ 1.8 (s, 12H)	$\delta$ 140.27, 137.28, 134.47, 131.94, 129.22, 128.38, 15.98	602.4	Anal. (C <sub>22</sub> H <sub>22</sub> Br <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 43.87, H 3.68, Br 26.53, N 4.65, O 10.62, S 10.65; found, (%) C 43.97, H 3.60, Br 26.55, N 4.75, O 10.54, S 10.47
<b>51</b> Yellow solid	263-265	$\delta$ 9.73 (s, 2H, NH x 2), $\delta$ 7.9 (d, J = 7.87 2H), $\delta$ 7.75 (s, 2H), $\delta$ 7.65 (d, J = 7.60 2H) 1.8 (s, 12H)	$\delta$ 141.69, 131.95, 131.66, 128.06, 126.49 16.02	582.3	Anal. (C <sub>22</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 45.37, H 3.46, Cl 24.35, N 4.81, O 10.99, S 11.01; found, (%) C 45.54, H 3.60, Cl 24.55, N 4.78, O 10.74, S 10.98
<b>52</b> Yellow solid	256-258 (dec)	$\delta$ 9.83 (s, 2H, NH x 2), $\delta$ 8.0 (s, 2H), $\delta$ 7.55 (s, 4H), $\delta$ 1.8 (s, 12H)	$\delta$ 135.26, 132.12, 124.82, 15.96	582.3	Anal. (C <sub>22</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 45.37, H 3.46, Cl 24.35, N 4.81, O 10.99, S 11.01; found, (%) C 45.52, H 3.60, Cl 24.55, N 4.75, O 10.89, S 10.89

<b>53</b> White solid	198-200	7.90 (d, J = 7.95 Hz, 4H), δ 7.80 (d, J = 7.85 Hz, 4H), δ 6.82 (s, 2H, NH x 2)	δ 166.86, 164.33, 134.15, 131.60, 117.01	496.4	Anal. (C <sub>18</sub> H <sub>10</sub> F <sub>6</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 43.55, H 2.03, F 22.96, N 5.64, O 12.89, S 12.92; found, (%) C 43.80, H 2.14, F 23.0, N 5.62, O 13.09, S 12.65
<b>54</b> White solid	253-255	δ 8.0 (d, J = 7.95 Hz, 4H), δ 7.6 (d, J = 7.58 Hz, 4H), δ 6.80 (s, 2H, NH x 2)	δ 145.63, 143.22, 132.73, 130.09	618.2	Anal. (C <sub>18</sub> H <sub>14</sub> F <sub>4</sub> Br <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 34.97, H 1.63, F 12.29, Br 25.85, N 4.53, O 10.35, S 10.37; found, (%) C 35.0, H 1.69, F 12.35, Br 25.72, N 4.48, O 10.41, S 10.33
<b>56</b> Tan solid	248-250	δ 10.2 (s, 2H, NH x 2), δ 7.6 (d, J = 7.74 Hz, 4H), δ 7.6 (m, 8H), δ 7.25 (s, 2H), δ 7.1 (s, 2H) δ 3.74 (s, 2H)	δ 156.84, 148.24, 143.77, 138.98, 136.06, 132.73, 127.54, 125.38, 120.0, 119.11, 117.17, 106.86, 38.81	476.6	Anal. (C <sub>22</sub> H <sub>22</sub> Br <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 43.87, H 3.68, Br 26.53, N 4.65, O 10.62, S 10.65; found, (%) C 43.97, H 3.60, Br 26.55, N 4.75, O 10.54, S 10.47
<b>57</b> Tan solid	200-202 (dec)	δ 10.5 (s, 2H, NH x 2), δ 7.7 (d, J = 7.68 Hz, 6H), δ 7.4 (s, 2H), δ 7.19 (d, J = 7.09, 2H), δ 3.89 (s, 2H)	δ 154.23, 152.21, 145.65, 139.34, 136.44, 136.36, 121.90, 121.32, 119.82, 113.49, 37.47	634.4	Anal. (C <sub>25</sub> H <sub>14</sub> F <sub>6</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 51.37, H 2.41, F 19.50, N 4.79, O 10.95, S 10.97; found, (%) C 51.19, H 2.33, F 19.79, N 4.69, O 10.89, S 10.90
<b>58</b> Tan solid	212-214 (dec)	δ 10.32 (s, 2H, NH x 2), δ 7.78 (d, J = 7.71 Hz, 4H), δ 7.62 (t, J = 7.59, 6H), δ 7.55 (s, 2H), δ 7.25 (d, J = 7.20, 2H) δ 3.89 (s, 2H)	δ 145.37, 140.09, 139.30, 140.02, 138.96, 136.99, 133.10, 129.88, 129.63, 127.83, 121.42, 121.08, 119.34, 37.42	545.5	Anal. (C <sub>25</sub> H <sub>22</sub> Br <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 47.33, H 2.86, Br 25.19, N 4.42, O 10.09, S 10.11; found, (%) C 47.0, H 2.86, Br 25.40, N 4.42, O 10.0, S 10.11,
<b>59</b> Tan solid	203-205 (dec)	δ 10.5 (s, 2H, NH x 2), δ 7.7 (d, J = 7.67 Hz, 10H), δ 7.3 (s, 2H), δ 7.1 (d, J = 7.06, 2H), δ 3.85 (s, 2H)	δ 143.99, 141.16, 133.68, 131.25, 120.23, 119.47, 117.58, 121.45, 121.06, 36.55	624.2	Anal. (C <sub>25</sub> H <sub>18</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 52.05, H 3.33, Cl 13.0, N 5.14, O 11.73, S 11.76; found, (%) C 54.98, H 3.37, Cl 12.97, N 5.21, O 11.71, S 11.99
<b>60</b> Tan solid	210-212 (dec)	δ 10.4 (s, 2H, NH x 2), δ 7.8 (t, J = 7.74 Hz, 4H), δ 7.65 (t, J = 7.62Hz, 6H), δ 7.32 (d, J = 7.28Hz, 2H), δ 7.2 (d, J = 7.07, 2H), δ 3.75 (s, 2H)	δ 143.96, 138.17, 137.67, 137.06, 135.79, 129.31, 128.53, 120.18, 119.45, 117.51, 36.31	545.5	Anal. (C <sub>25</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> ); calc. (%) C 55.05, H 3.33, Cl 13.0, N 5.14, O 11.73, S 11.76; found, (%) C 54.98, H 3.36, Cl 13.05, N 5.20, O 11.65, S 12.01