RESEARCH ARTICLE



Synthesis, cytotoxicity and QSAR study of *N*-tosyl-1,2,3,4tetrahydroisoquinoline derivatives

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Abstract 1-Substituted-*N*-tosyl-1,2,3,4-tetrahydroisoquinoline analogs (**4a–4l**) were synthesized using the modified Pictet–Spengler reaction and evaluated for cytotoxicity. All tetrahydroisoquinolines displayed cytotoxicity against MOLT-3 cell lines, except for *p*-methoxy analog **4d**. Interestingly, the *o*-hydroxy derivative **4k** was shown to be the most potent cytotoxic against HuCCA-1, A-549 and MOLT-3 cell lines. The lowest IC₅₀ value of 1.23 μ M was observed for MOLT-3 cells. Trimethoxy analog **4f** exerted the most potent activity against HepG2 with an IC₅₀ of 22.70 μ M, which is lower than the reference drug, etoposide. QSAR studies showed that total symmetry index (Gu), 3D-MoRSE (Mor31v and Mor32u) and 3D Petitjean index (PJI3) were the most important descriptors accounting for the observed cytotoxicities. The most potent cytotoxic compound (**4k**) against

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MOLT-3 had the highest Gu value, correspondingly the inactive *p*-methoxy analog (4d) had the lowest Gu value. On the other hand, the highest molecular mass compound (4f) was shown to be the most potent cytotoxic against HepG2 cells. The studies disclose that tetrahydroisoquinolines 4f and 4k are potentially interesting lead pharmacophores that should be further explored. The QSAR models provided insights into the physicochemical properties of the investigated compounds.

Introduction

Isoquinoline is an important class of heterocyclic scaffold which is frequently found in many natural sources (Bentley 1998). Natural and synthetic isoquinoline alkaloids exhibit a variety of pharmacological properties including anticancer, antimicrobial, antimalarial and anti-HIV activities (Bermejo et al. 2002; Cui et al. 2006; González et al. 2007a; Iwasa et al. 2001; Pingaew et al. 2013; Saitoh et al. 2006; Scott and Williams 2002; Siengalewicz et al. 2008).

Sulfonamide moiety is present in diverse biologically active molecules (Scozzafava et al. 2003). Aryl/heteroaryl sulfonamides are known to exert antitumor properties. Some of the modified analogs such as E7010 (ABT-751), HMN-214, T138067 and T900607 have been evaluated in clinical trials (Hu et al. 2008). Various biological studies of a series of 1,2,3,4-tetrahydroisoquinolines based sulfonamide have been previously documented. They have been revealed to act as phenylethanolamine *N*-methyltransferase inhibitors (Grunewald et al. 2005), matrix metalloproteinase inhibitors

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(Ma et al. 2004; Matter and Schwab 1999; Matter et al. 2002), carbonic anhydrase inhibitors (Gitto et al. 2009, 2010), bradykinin-1 antagonists (Huszár et al. 2008) as well as potential ligands of the delta opioid receptor (Barn et al. 2001; Bourdier et al. 2007). Considering the interesting bioactivities of the isoquinolines and sulfonamides has prompted us to design and synthesize a series of 1,2,3,4tetrahydroisoquinoline derivatives bearing the sulfonamide entity through the use of simple and efficient method.

The Pictet-Spengler reaction which involves the cyclization of iminium ion derived from the condensation of β -arylethylamine derivatives with aldehydes, is one of the most important strategies for the construction of tetrahydroisoquinoline (Cox and Cook 1995; Larghi et al. 2005). However, this method has a limitation regarding its prerequisite of electron donating substituents. Modifications to the original approach by means of using the masked carbonyls and electron withdrawing groups, such as acyl or sulforyl moieties, bound to the starting β -arylethylamine have been developed (Ito and Tanaka 1977; Lukanov et al. 1987; Orazi et al. 1986; Silveira et al. 1999, 2003, 2006). In this article, we employed the modified Pictet-Spengler reaction for the synthesis of a series of N-tosyl-1,2,3,4tetrahydroisoquinolines, by exploring the effects of various substituents at the C-1 position of the tetrahydroisoquinoline system. It is expected that not only the sulforyl group affects the cyclization by increasing the electrophilicity of an iminium intermediate, but the sulfonyl group could also be a useful feature governing the bioactivity. Although some N-sulfonyltetrahydroisoquinoline analogs have been previously known, however their cytotoxic activities have apparently not yet been published. In this regard, the cytotoxicities of N-sulfonyl-1,2,3,4-tetrahydroisoquinolines were investigated. To provide insights into the effect that substituents at the C-1 position has on their cytotoxicities, the quantitative structure-activity relationship (QSAR) of the compounds was investigated.

Materials and methods

Column chromatography was carried out using silica gel 60 (70–230 mesh ASTM). Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F_{254} aluminium sheets. ¹H- and ¹³C-NMR spectra were recorded on a Bruker AVANCE 300 NMR spectrometer (operating at 300 MHz for ¹H and 75 MHz for ¹³C). FTIR were obtained using a universal attenuated total reflectance attached on a Perkin–Elmer Spectrum One spectrometer. Mass spectra were recorded on a Bruker Daltonics (microTOF). Melting points were determined using a Griffin melting point apparatus and were uncorrected.

General procedure for the synthesis of *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines (**4a–4l**)

A mixture of sulfonamide **3** (0.67 mmol) and appropriate aldehyde (0.72 mmol) in formic acid or trifluoroacetic acid (15 mL) was stirred under reflux for 0.5–27 h and then allowed to cool to room temperature. The reaction mixture was added to 30 mL of ice cool water and the product was extracted with CH₂Cl₂ (2 × 30 mL). Combined extracts were washed with saturated aqueous NaHCO₃, dried (anh. Na₂SO₄) and evaporated to dryness under reduced pressure. The crude product was purified by silica gel column chromatography.

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[(4methylphenyl)sulfonyl]-isoquinoline (4a)

85 % yield. mp 144–145 °C [144–145 °C (Ito and Tanaka 1977)]. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.40 (s, 3H, ArCH₃), 2.82 (t, J = 5.8 Hz, 2H, C4), 3.30 (t, J = 5.8 Hz, 2H, C3), 3.79, 3.80 (2 s, 6H, 2 × OCH₃), 4.14 (s, 2H, C-1), 6.48 (s, 1H, C5-Ar*H*), 6.52 (s, 1H, C8-Ar*H*), 7.30 (d, J = 8.0 Hz, 2H, C3'-Ar*H*₂), 7.69 (d, J = 8.0 Hz, 2H, C2'-Ar*H*₂); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 21.5, 28.4, 43.8, 47.2, 55.9, 109.0, 111.3, 123.4, 125.0, 127.7, 129.7, 133.3, 143.6, 147.7, 147.9. IR (UATR) cm⁻¹: 1612, 1518, 1342, 1161, 1116. TOF-MS *m*/*z*: 348.1271 (Calcd for C₁₈H₂₂NO₄S: 348.1270).

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[(4methylphenyl)sulfonyl]-1-methylisoquinoline (**4b**)

89 % yield. mp: 150–151 °C [150 °C (Hazebroucq 1966)]. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 1.43 (d, J = 6.7 Hz, 3H, CHCH₃), 2.34 (s, 3H, ArCH₃), 2.36–2.68 (m, 2H, C4), 3.30–3.41, 3.75–3.92 (m, 2H, C3), 3.77, 3.81 (2 s, 6H, 2 × OCH₃), 5.03 (q, J = 6.7 Hz, 1H, C1), 6.42, 6.49 (2 s, 2H, C5-ArH, C8-ArH), 7.17 (d, J = 7.8 Hz, 2H, C3'-ArH₂), 7.64 (d, J = 7.8 Hz, 2H, C2'-ArH₂); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 21.4, 23.3, 27.3, 38.5, 51.7, 55.9, 56.0, 109.5, 111.4, 124.7, 126.9, 129.5, 129.7, 138.1, 143.0, 147.6, 147.8. IR (UATR) cm⁻¹: 1612, 1518, 1323, 1154, 1125. TOF-MS *m*/*z*: 362.1423 (Calcd for C₁₉H₂₄NO₄S: 362.1421).

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[(4methylphenyl)sulfonyl]-1-phenylisoquinoline (4c)

92 % yield. mp: 122–123 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.36 (s, 3H, CH₃), 2.40–2.65 (m, 2H, C4), 3.15–3.30, 3.71–3.90 (m, 2H, C3), 3.78, 3.84 (2 s, 6H, 2 × OCH₃), 6.19 (s, 1H, C1), 6.46 (s, 2H, C5-ArH, C8-ArH), 7.13 (d, J = 8.0 Hz, 2H, C3"-ArH₂), 7.19–7.31 (m,

5H, C2'-Ar*H*₂, C3'-Ar*H*₂, C4'-Ar*H*), 7.58 (d, J = 8.2 Hz, 2H, C2"-Ar*H*₂); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 21.4, 26.1, 38.7, 55.8, 55.9, 58.8, 110.7, 111.2, 125.6, 126.0, 127.0, 127.6, 128.2, 128.8, 129.3, 137.9, 141.5, 143.0, 147.5, 148.2. IR (UATR) cm⁻¹: 1611, 1516, 1336, 1157, 1116. TOF-MS *m*/*z*: 424.1583 (Calcd for C₂₄H₂₆NO₄S: 424.1577).

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[(4methylphenyl)sulfonyl]-1-(4-methoxyphenyl)isoquinoline (**4d**)

35 % yield. mp: 119–120 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.36 (s, 3H, CH₃), 2.40–2.65 (m, 2H, C4), 3.12–3.30, 3.70–3.90 (m, 2H, C3), 3.78, 3.80, 3.84 (3 s, 9H, 3 × OCH₃), 6.16 (s, 1H, C1), 6.45 (s, 2H, C5-ArH, C8-ArH), 6.81 (d, J = 8.0 Hz, 2H, C3"-ArH₂), 7.13 (d, J = 7.7 Hz, 4H, C2'-ArH₂, C3'-ArH₂), 7.59 (d, J = 8.2 Hz, 2H, C2"-ArH₂); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 21.4, 26.1, 38.5, 55.3, 55.8, 55.9, 58.3, 110.7, 111.2, 113.5, 125.9, 127.0, 129.3, 130.0, 133.8, 138.0, 142.9, 147.5, 148.1, 159.1. IR (UATR) cm⁻¹: 1609, 1509, 1336, 1157, 1118. TOF-MS *m*/*z*: 454.1694 (Calcd for C₂₅H₂₈NO₅S: 454.1683).

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[(4methylphenyl)sulfonyl]-1-(3-hydroxy-4-methoxyphenyl)isoquinoline (*4e*)

54 % yield. mp: 171–172 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.30 (s, 3H, CH₃), 2.00–2.60 (m, 2H, C4), 3.12–3.30, 3.70–3.90 (m, 2H, C3), 3.73, 3.78, 3.83 (3 s, 9H, 3 × OCH₃), 6.06 (s, 1H, C1), 6.39, 6.40 (2 s, 2H, C5-ArH, C8-ArH), 6.63–6.76 (m, 3H, C2'-ArH, C5'-ArH, C6'-ArH), 7.07 (d, J = 8.1 Hz, 2H, C3''-ArH₂), 7.54 (d, J = 8.1 Hz, 2H, C2''-ArH₂). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 21.4, 26.1, 38.6, 55.8, 55.9, 56.0, 58.4, 110.2, 110.7, 111.2, 115.1, 120.8, 125.9, 127.0, 129.2, 134.9, 138.0, 142.9, 145.2, 146.0, 147.5, 148.1. IR (UATR) cm⁻¹: 3433, 1596, 1509, 1318, 1157, 1113. TOF-MS *m/z*: 470.1629 (Calcd for C₂₅H₂₈NO₆S: 470.1632).

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[(4methylphenyl)sulfonyl]-1-(3,4,5-trimethoxyphenyl)isoquinoline (**4***f*)

85 % yield. mp: 174–175 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.31 (s, 3H, CH₃), 2.38–2.65 (m, 2H, C4), 3.15–3.30, 3.70–3.90 (m, 2H, C3), 3.69, 3.76, 3.80, 3.81 (4 s, 15H, $5 \times OCH_3$), 6.05 (s, 1H, C1), 6.36, 6.42, 6.44 (3 s, 4H, C5-Ar*H*, C8-Ar*H*, C2'-Ar*H*₂), 7.10 (d, J = 8.0 Hz, 2H, C3"-Ar*H*₂), 7.56 (d, J = 8.2 Hz, 2H, C2"-Ar*H*₂); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 21.4, 26.3, 38.9, 55.8, 56.0, 56.1, 58.9, 60.8, 106.2, 110.8, 111.2, 125.4, 126.1, 127.0, 129.3, 137.2, 138.1, 143.0, 147.4, 148.2, 152.9. IR

(UATR) cm⁻¹: 1590, 1518, 1323, 1158, 1115. TOF-MS m/z: 514.1912 (Calcd for C₂₇H₃₂NO₇S: 514.1894).

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[(4-

methylphenyl)sulfonyl]-1-(4-hydroxyphenyl)-isoquinoline (*4g*)

34 % yield. mp: 146–147 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.31 (s, 3H, CH₃), 2.25–2.55 (m, 2H, C4), 3.10–3.22, 3.65–3.80 (m, 2H, C3), 3.73, 3.78 (2 s, 6H, 2 × OCH₃), 6.10 (s, 1H, C1), 6.39, 6.40 (2 s, 2H, C5-ArH, C8-ArH), 6.70 (d, J = 8.5 Hz, 2H, C3'-ArH₂), 7.02 (d, J = 8.5 Hz, 2H, C2'-ArH₂), 7.08 (d, J = 8.1 Hz, 2H, C3''-ArH₂), 7.54 (d, J = 8.1 Hz, 2H, C2''-ArH₂); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 21.4, 26.0, 38.4, 55.8, 56.0, 58.4, 110.7, 111.2, 115.1, 125.9, 127.0, 129.3, 130.2, 133.5, 137.9, 143.1, 147.4, 148.1, 155.4. IR (UATR) cm⁻¹: 3428, 1611, 1512, 1320, 1154, 1116. TOF-MS *m/z*: 440.1538 (Calcd for C₂₄H₂₆NO₅S: 440.1532).

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[(4methylphenyl)sulfonyl]-1-(4-hydroxy-3-methoxyphenyl)-

isoquinoline (**4h**)

57 % yield. mp: 125–126 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.35 (s, 3H, CH₃), 2.40–2.64 (m, 2H, C4), 3.15–3.30, 3.80–3.90 (m, 2H, C3), 3.78, 3.83, 3.84 (3 s, 9H, 3 × OCH₃), 6.11 (s, 1H, C1), 6.42–6.48 (m, 3H, C5-ArH, C8-ArH, C6'-ArH), 6.76 (d, J = 8.2 Hz, 1H, C5'-ArH), 6.92 (d, J = 1.7 Hz, 2H, C2'-ArH), 7.13 (d, J = 8.2 Hz, 2H, C3''-ArH₂), 7.59 (d, J = 8.2 Hz, 2H, C2''-ArH₂); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 21.4, 26.1, 38.5, 55.8, 55.9, 58.7, 110.7, 111.1, 111.5, 113.5, 121.8, 125.7, 126.0, 127.0, 129.3, 133.5, 138.1, 143.0, 145.2, 146.5, 147.4, 148.1. IR (UATR) cm⁻¹: 3432, 1611, 1513, 1321, 1156. TOF-MS *m*/*z*: 470.1636 (Calcd for C₂₅H₂₈NO₆S: 470.1632).

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[(4methylphenyl)sulfonyl]-1-(4-hydroxy-3,5dimethoxyphenyl)-isoquinoline (**4i**)

62 % yield. mp: 148–149 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.31 (s, 3H, CH₃), 2.38–2.65 (m, 2H, C4), 3.15–3.28, 3.70–3.85 (m, 2H, C3), 3.72, 3.74, 3.80 (3 s, 6H, 4 × OCH₃), 5.48 (s, 1H, C1), 6.35 (s, 2H, C2'-ArH₂), 6.41, 6.42 (s, 2H, C5-ArH, C8-ArH), 7.10 (d, J = 8.2 Hz, 2H, C3"-ArH₂), 7.55 (d, J = 8.2 Hz, 2H, C2"-ArH₂). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 21.4, 26.3, 38.7, 55.8, 56.0, 56.3, 58.9, 105.9, 110.8, 111.1, 125.6, 126.1, 127.0, 129.3, 132.7, 134.3, 138.1, 143.0, 146.7, 147.4, 148.1. IR (UATR) cm⁻¹: 3435, 1612, 1515, 1319, 1156, 1110. TOF-MS *m*/*z*: 500.1729 (Calcd for C₂₆H₃₀NO₇S: 500.1738).

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[(4methylphenyl)sulfonyl]-1-(4-bromophenyl)isoquinoline (**4j**)

84 % yield. mp: 120–121 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.32 (s, 3H, CH₃), 2.30–2.60 (m, 2H, C4), 3.05–3.20, 3.65–3.85 (m, 2H, C3), 3.74, 3.80 (2 s, 6H, 2 × OCH₃), 6.09 (s, 1H, C1), 6.37, 6.41 (2 s, 2H, C5-ArH, C8-ArH), 7.06 (d, J = 8.5 Hz, 2H, C2'-ArH₂), 7.09 (d, J = 8.5 Hz, 2H, C3'-ArH₂), 7.37 (d, J = 8.0 Hz, 2H, C3''-ArH₂), 7.54 (d, J = 8.2 Hz, 2H, C2''-ArH₂). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 21.5, 26.1, 38.8, 55.8, 55.9, 58.2, 110.5, 111.2, 121.8, 125.0, 126.0, 127.0, 129.4, 130.5, 131.4, 137.7, 140.7, 143.2, 147.6, 148.3. IR (UATR) cm⁻¹: 1611, 1516, 1339, 1158, 1117. IR (UATR) cm⁻¹: 1611, 1516, 1339, 1158, 1117. TOF-MS *m*/*z*: 502.0676 (Calcd for C₂₄H₂₅BrNO₄S: 502.0682).

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[(4methylphenyl)sulfonyl]-1-(2-hydroxyphenylisoquinoline (**4k**)

52 % yield. mp: 96–97 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.30 (s, 3H, *CH*₃), 2.30–2.60 (m, 2H, C4), 3.17–3.32, 3.77–3.92 (m, 2H, C3), 3.75, 3.85 (2 s, 6H, 2 × OC*H*₃), 6.27 (s, 1H, C1), 6.32, 6.33 (2 s, 2H, C5-Ar*H*, C8-Ar*H*), 6.46 (d, J = 7.6 Hz, 1H, C3'-ArH), 6.70 (t, J = 7.6 Hz, 1H, C5'-ArH), 7.05 (d, J = 7.6 Hz, 1H, C6'-ArH), 7.08 (d, J = 8.2 Hz, 2H, C3''-Ar*H*₂), 7.20 (t, J = 7.6 Hz, 1H, C4'-ArH), 7.61 (d, J = 8.2 Hz, 2H, C2''-Ar*H*₂). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 21.5, 25.1, 38.4, 54.7, 55.8, 55.9, 110.3, 110.9, 117.9, 119.7, 124.2, 125.7, 126.4, 127.1, 129.5, 129.9, 130.0, 136.4, 143.9, 147.7, 148.3, 155.4. IR (UATR) cm⁻¹: 3405, 1611, 1517, 1322, 1151, 1119. TOF-MS *m*/*z*: 440.1531 (Calcd for C₂₄H₂₆NO₅S: 440.1526).

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[(4methylphenyl)sulfonyl]-1-(3-pyridyl)-isoquinoline (**4l**)

94 % yield. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.31 (s, 3H, CH₃), 2.40–2.60 (m, 2H, C4), 3.05–3.20, 3.80–3.90 (m, 2H, C3), 3.71, 3.78 (2 s, 6H, 2 × OCH₃), 6.17 (s, 1H, C1), 6.36, 6.44 (2 s, 2H, C5-ArH, C8-ArH), 7.12 (d, J = 7.9 Hz, 2H, C3"-ArH₂), 7.45–7.60 (m, 3H, C5'-ArH, C2"-ArH₂), 7.97 (d, J = 7.7 Hz, 1H, ArH), 8.35 (s, 1H, ArH), 8.63 (d, J = 4.1 Hz, 1H, ArH). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 21.4, 26.0, 39.5, 55.9, 56.0, 56.5, 110.0, 111.6, 122.6, 125.5, 126.2, 127.0, 129.7, 136.7, 140.8, 141.8, 143.8, 143.9, 144.0, 148.1, 149.0. IR (UATR) cm⁻¹: 1688, 1611, 1517, 1338, 1158, 1115. TOF-MS *m/z*: 425.1536 (Calcd for C₂₃H₂₅N₂O₄S: 425.1530).

Cytotoxic assay

The cytotoxic assay was performed as previously described by Tengchaisri and co-workers (Tengchaisri et al., 1998). Briefly, cell lines suspended in RPMI 1640 containing 10 % fetal bovine serum (FBS) were seeded at 1×10^4 cells (100 µL) per well in a 96-well plate, and incubated in humidified atmosphere, 95 % air, 5 % CO_2 at 37 °C. After 24 h, additional medium (100 µL) containing the test compound and vehicle was added to a final concentration of 50 µg/mL, 0.2 % dimethyl sulfoxide (DMSO), and further incubated for 3 days. After that, the cells were fixed with EtOH-H₂O (95:5, v/v), stained with crystal violet solution, and lysed with a solution of 0.1 N HCl in MeOH. The absorbance was measured at 550 nm. The number of surviving cells was determined from the absorbance. Etoposide and/or doxorubicin were used as the reference drugs.

Computational analysis

Data set

The IC₅₀ (μ M) values of cytotoxicity against HepG2 and MOLT-3 cell lines were converted to pIC₅₀ by taking the negative logarithm to the base of 10 of the IC₅₀ values. The molecular structures of the 12 compounds investigated in this study are presented in Fig. 1.

Quantum chemical and molecular descriptors calculation

Molecular structures of the compounds were drawn using GaussView (Dennington II et al. 2003). Geometric optimization was initially performed at the semi-empirical method AM1 (Austin Model 1) and finally optimized at the DFT level using Becke's three-parameter hybrid method using the Lee-Yang-Parr correlation functional (B3LYP) together with the 6-31 g(d) basis set in the Gaussian 03 W package (Frisch et al. 2004). Quantum chemical descriptors were obtained from the optimized structure, which included: total energy (E_{total}) , highest occupied molecular orbital energy (E_{HOMO}) , lowest unoccupied molecular orbital energy (E_{LUMO}), total dipole moment (μ) of the molecule, electron affinity (EA), the ionization potential (IP), energy difference of HOMO and LUMO $(E_{HOMO} - E_{LUMO})$, Mulliken electronegativity (χ), hardness (η), electrophilicity (ω), softness (S), electrophilic index (ω_i), highest negative charge (Q^{-}) , highest positive charge (Q^{+}) and mean absolute atomic charge (Q_m) (Karelson et al. 1996; Parr et al. 1978, 1999; Parr and Pearson 1983; Thanikaivelan et al. 2000). Furthermore, an additional set of 3,224 descriptors were obtained from the Dragon software (Talete 2007) using the optimized structure as input data. The





Reagents and conditions: (a) Na₂CO₃, CH₂Cl₂ (b) paraformaldehyde, HCOOH, reflux for **4a**; RCHO, TFA, reflux for **4b-4l**



Fig. 1 Molecular structures of *N*-sulfonyl-1,2,3,4tetrahydroisoquinolines (**4a–4l**)

molecular descriptors from Dragon can be classified into 22 categories: 48 Constitutional descriptors, 119 Topological descriptors, 47 Walk and path counts, 33 Connectivity indices, 47 Information indices, 96 2D autocorrelation, 107 Edge adjacency indices, 64 Burden eigenvalues, 21 Topological charge indices, 44 Eigenvalue-based indices, 41 Randic molecular profiles, 74 Geometrical descriptors, 150 RDF descriptors, 160 3D-MoRSE descriptors, 99 WHIM descriptors, 197 GETAWAY descriptors, 154 Functional

group counts, 120 Atom-centred fragments, 14 Charge descriptors, 29 Molecular properties, 780 2D binary fingerprints and 780 2D frequency fingerprints.

Multivariate analysis

The independent variables are comprised of quantum chemical and molecular descriptors while the dependent variables are the cytotoxicity pIC_{50} values. Multivariate

analysis was performed using multiple linear regression (MLR) using Waikato Environment for Knowledge Analysis (Weka), version 3.4.5. (Witten et al. 2011).

Multiple linear regression

The MLR models were calculated to obtain the following equation:

$$Y = B_0 + \sum B_n X_n \tag{1}$$

where Y is the pIC₅₀ values of the compounds, B_0 is the intercept, and B_n are the regression coefficients of the descriptors X_n .

Data sampling

Leave-one-out cross-validation (LOO-CV) was used as a data sampling approach to separate the data set as a training set and testing set. LOO-CV is a practical and reliable method for testing significance. Briefly, one data sample was left out and used as the testing set and the remaining N - 1 samples were used as the training set. In this respect, each member of the data set had a chance to be used as the testing set to predict the dependent variable (Y).

Statistical analysis

Sample outliers were identified using ± 2 standardized residual as the cutoff criteria where values exceeding the cutoff will be removed. Standardization of the residuals (difference of actual and predicted values) was calculated according to the following equation:

$$x_{ij}^{stn} = \frac{x_{ij} - \bar{x}_j}{\sum_{i=1}^{N} (x_{ij} - \bar{x}_j)^2 / N}$$
(2)

where x_{ij}^{stn} is the standardized value, x_{ij} is the value of each sample, \bar{x}_j is the mean of each descriptors and N is the sample size of the data set.

Calculated descriptors from Dragon that are constant or near-constant were implied to be redundant and were, therefore, removed using the Unsupervised Forward Selection algorithm of UFS, version 1.8. The UFS algorithm was previously described by Whitley et al. (2000) and Nantasenamat et al. (2005). Furthermore, significant descriptors were selected using stepwise regression as performed by SPSS Statistics 18.0 (SPSS Inc., USA). Intercorrelation among the descriptors was calculated using Pearson's correlation coefficient as implemented in SPSS Statistics 18.0 (SPSS Inc., USA).

Evaluation of the predictive ability of the QSAR models were assessed using the following statistical parameters: correlation coefficient (r), square of correlation coefficient (R^2), root mean square error (RMSE), predictive power of

the model (Q^2) , F value and critical F value (Alves et al. 2001; Nantasenamat et al. 2008a, 2009, 2010).

Results and discussion

Chemistry

4-Methyl-N-(2-(3,4-dimethoxyphenyl)ethyl)-benzenesulfonamide 3 was readily prepared by the condensation of homoveratrylamine 1 with *p*-toluenesulfonyl chloride 2 in methylene chloride catalyzed by sodium carbonate as shown in Scheme 1 (Pingaew et al. 2013). With the availability of the starting benzenesulfonamide 3 in hand, we then investigated the condensation of key sulfonamide 3 with various aldehydes under Brönsted acid condition (i.e. HCOOH, CF₃COOH). The reactions readily furnished the cyclization product, N-tosyl-1,2,3,4-tetrahydroisoquinoline analogs (4) in moderate to good yields (34-94 %) as shown in Table 1. The results showed that the synthesis of N-sulfonyl-1,2,3,4tetrahydroisoquinolines depended on the reactivity of aldehyde. The more reactive aldehyde such as formaldehyde, could be obtained in mild formic acid (entry 1) instead of the strong acid, TFA, which was employed in the cases of other aldehydes (entries 2-12). The formation of the desired isoquinolines (4) was confirmed by ¹H NMR spectra which showed the absence of the NH proton, while the singlet of methine proton at δ in the range of 5–7 ppm was displayed indicating that the cyclized products (4c-4l) were formed. In addition, the singlet of methylene proton at δ 4.14 ppm and the quartet of methine proton at δ 5.03 ppm were observed

 Table 1
 Chemical yield of the N-sulfonyl-1,2,3,4-tetrahydroisoquinolines (4a-4l)

| Entry | Isoquinoline | R | Time (h) | Yield (%) |
|----------------|--------------|--|-------------|--------------|
| 1 ^a | 4 a | Н | 1 | 85 |
| 2 | 4b | Me | 0.5 | 89 |
| 3 | 4c | C ₆ H ₅ | 2 | 92 |
| 4 | 4d | 4-OMe-C ₆ H ₄ | 27 | 35 |
| 5 | 4e | 3-OH,4-OMe-C ₆ H ₃ | 5 | 54 |
| 6 | 4f | 3,4,5-(OMe) ₃ -C ₆ H ₃ | 12 | 85 |
| 7 | 4g | $4-OH-C_6H_4$ | 27 | 34 |
| 8 | 4h | 3-OMe,4-OH-C ₆ H ₃ | 5 | 57 |
| 9 | 4i | 3,5-(OMe) ₂ ,4-OH-C ₆ H ₃ | 8 | 62 |
| 10 | 4j | 4-Br-C ₆ H ₄ | 2 | 84 |
| 11 | 4k | $2-OH-C_6H_4$ | 27 | 52 |
| 12 | 41 | $3-C_5H_4N$ | 5 | 94 |

TFA, reflux for 4b-4l

^a HCOOH, reflux for 4a

for 1-unsubstituted isoquinoline 4a and 1-methylisoquinoline 4b, respectively. The structures of all obtained compounds were further supported by ¹³C NMR, 2D NMR, IR as well as HRMS.

Cytotoxic activity

For an assessment of the cytotoxicity (Tengchaisri et al. 1998), the synthesized isoquinoline analogs 4a-4l (Fig. 1) were evaluated against HuCCA-1, HepG2, A549 and MOLT-3 human cancer cell lines as summarized in Table 2. All of the tested compounds displayed inhibition activities against MOLT-3 cell lines, except for p-methoxy analog 4d. The analog 4d also exhibited no cytotoxicity against other tested cell lines. All the investigated cells were inhibited by analogs 4k and 4l. Interestingly, the analog 4k was shown to be the most potent cytotoxic against HuCCA-1, A549 and MOLT-3 cells. In particular, compound **4k** had the lowest IC₅₀ value of 1.23 μ M against MOLT-3 cell. On the other hand, trimethoxy analog 4f was the most potent compound (IC₅₀ = 22.70 μ M) against HepG2 cell and was stronger than the reference drug, etoposide. These cytotoxics contain the common core structure of N-tosyl-1,2,3,4-tetrahydroisoquinoline, but with different substituents (R) at the C-1 position. It was noted that high cytotoxicity (MOLT-3) was achieved when R was aromatic (phenyl) as compared to alkyl (CH₃) and H substituents. This could be due to hydrophobic effect that

enhances its absorption to cells. Comparable result was also observed for heterocyclic pyridyl group at C-1 as seen for analog **4**l. Among the tested analogs, *p*-methoxy compound (4d, R = p-OMeC₆H₄) was shown to be an inactive cytotoxic (IC₅₀ > 110.09 μ M). Remarkable cytotoxicity was found when R displayed the p-OHC₆H₄ (4g, $IC_{50} = 20.06 \ \mu M$) and p-BrC₆H₄ (**4j**, $IC_{50} = 22.69 \ \mu M$) substituents. However, unsubstituted phenyl analog (4c) exerted higher cytotoxic effect (IC₅₀ 15.49 μ M) than the substituted p-OH (4g) and p-Br (4j) compounds. Introduction of di-OMe groups to 3- and 5-positions of the analog 4g furnished compound 4i with lower cytotoxicity (IC₅₀ 40.61 μ M) than the parent compound 4g. It was notable that 3,4,5-trimethoxy analog 4f exhibited greater activity (IC₅₀ 9.24 µM) than the trisubstituted 3,5-dimethoxy-4-hydroxyphenyl analog 4i. It is likely that the trimethoxy analog 4f bears appropriate lipophilic moiety for cell absorption when compared to 3,4,5- trisubstituted phenyl analog 4i. It was also observed that substituents at 3- and 3,5-positions of 4-hydroxyphenyl analog 4g provided analogs 4h and 4i, respectively, with decreasing cytotoxicities. Conversely, the inactive 4-OMe analog (4d) was changed to be active compounds 4e and 4f when the corresponding 3- and 3,5-substituents were placed on the phenyl group of 4d. Significant results were observed when the OH group was substituted on the ortho-position of the phenyl group as seen for the most potent analog 4k. Obviously, the o-OH analog 4k had 16-fold higher

 Table 2 Cytotoxic activity of compounds 4a-4l against four cancer cell lines

| Compound | Cytotoxic activity (IC | ₅₀ , µM) ^a | | |
|--------------------------|------------------------|----------------------------------|-------------------|-------------------|
| | HuCCA-1 | HepG2 | A549 | MOLT-3 |
| 4a | >143.62 | >143.62 | >143.62 | 65.58 ± 0.83 |
| 4b | >124.26 | 111.83 ± 7.07 | >124.26 | 55.81 ± 0.48 |
| 4c | >117.88 | >117.88 | >117.88 | 15.49 ± 1.08 |
| 4d | >110.09 | >110.09 | >110.09 | >110.09 |
| 4e | >106.35 | >106.35 | >106.35 | 36.67 ± 0.42 |
| 4f | >97.24 | 22.70 ± 0.58 | >97.24 | 9.24 ± 0.23 |
| 4g | >113.60 | 79.52 ± 2.65 | >113.60 | 20.06 ± 0.21 |
| 4h | >106.35 | 85.08 ± 7.07 | >106.35 | 41.20 ± 0.81 |
| 4i | >99.97 | 79.97 ± 9.50 | >99.97 | 40.61 ± 0.28 |
| 4j | >99.59 | >99.59 | >99.59 | 22.69 ± 0.05 |
| 4k | 43.17 ± 2.82 | 44.69 ± 4.72 | 56.80 ± 5.46 | 1.23 ± 0.07 |
| 41 | 72.92 ± 1.41 | 49.39 ± 3.60 | 117.61 ± 1.41 | 12.42 ± 0.33 |
| Etoposide ^b | ND | 27.18 ± 5.29 | ND | 0.041 ± 0.004 |
| Doxorubicin ^b | 0.64 ± 0.21 | 0.42 ± 0.03 | 0.70 ± 0.03 | ND |

Cancer cell lines are HuCCA-1 human cholangiocarcinoma cancer cells, HepG2 human hepatocellular carcinoma cell line, A549 human lung carcinoma cell line and MOLT-3 human lymphoblastic leukemia cell line

ND not determined

^a The assays were performed in triplicate

^b Etoposide and/or doxorubicin were used as the reference drugs

cytotoxicity than the *p*-OH compound **4g**. This could be assumed that o-OHC₆H₄ at C-1 is very important for the cytotoxic activity against MOLT-3 cells. It is reasonable to explain that OH group at the *o*-position may participate in the formation of intramolecular H-bond with the *N*-sulfonyl group of the target molecule **4k**.

QSAR modeling

Compounds that act as cytotoxics against cancer cell lines, particularly, MOLT-3 and HepG2 were selected for the study. Molecular structures of the compounds were constructed and optimized for calculating quantum chemical and molecular descriptors using Gaussian and Dragon software, respectively. Successful utilization of these descriptors in the development of QSAR models have previously been reported (Nantasenamat et al. 2007a, b, 2008b; Prachayasittikul et al. 2010; Suksrichavalit et al. 2009; Suvannang et al. 2011; Worachartcheewan et al. 2009, 2011, 2012). Descriptors were generated using DRAGON to yield 3,224 variables where constant or nearconstant descriptors were removed to obtain a set of 1,292 descriptors. The Dragon descriptor together with the set of 15 descriptors from Gaussian software were standardized according to Eq. (2) to further remove redundant descriptors using the UFS software. This resulted in a set of 11 descriptors which comprises of (i) Molecular properties: GVWAI-80, (ii) 2D autocorrelation indices: GATS6v, (iii) Geometrical descriptors: PJI3, (iv) WHIM descriptors: Gu, (v) 2D frequency fingerprints: F06[N-O], (vi) Atom-centred fragments: C-024 (vii) GETAWAY descriptors: R5e+ and R4u+, (viii) 3D-MoRSE descriptors: Mor31v and Mor32u and (ix) quantum chemical descriptors: LUMO. These descriptors were then subjected to stepwise MLR

 Table 3 The important descriptors and predicted cytotoxic activity of compounds 4a-4l against MOLT-3 cell lines

| Compound | Gu | Mor32u | Experimental activity (pIC ₅₀) | Predicted activity (pIC ₅₀) |
|-----------|-------|--------|--|--|
| 4a | 0.171 | -0.211 | -1.817 | -1.559 |
| 4b | 0.177 | -0.305 | -1.747 | -1.374 |
| 4c | 0.169 | -0.171 | -1.190 | -1.813 |
| 4d | 0.167 | -0.272 | -2.042 | -1.963 |
| 4e | 0.176 | -0.305 | -1.564 | -1.462 |
| 4f | 0.176 | -0.025 | -0.966 | -0.832 |
| 4g | 0.181 | -0.343 | -1.302 | -1.214 |
| 4h | 0.176 | -0.439 | -1.615 | -1.791 |
| 4i | 0.175 | -0.447 | -1.609 | -1.916 |
| 4j | 0.183 | -0.345 | -1.356 | -1.046 |
| 4k | 0.192 | -0.265 | -0.089 | -0.727 |
| 41 | 0.179 | -0.226 | -1.094 | -1.120 |

method to further select important descriptors using the SPSS software.

The significant descriptors for predicting the cytotoxic activity against MOLT-3 cell lines as obtained from stepwise MLR are displayed in Table 3. Two descriptors such as Mor32u (3D-MoRSE—signal 32/unweighted) and Gu (G total symmetry index/unweighted) were found to be responsible for cytotoxic activity against MOLT-3 cell. The descriptors were used to construct QSAR model using MLR according to Eq. (1). The QSAR equation (model 1) and model evaluations are displayed in Table 4. It was found that the r and RMS values obtained from the training set were 0.8899 and 0.2229, respectively, while the r and RMS values of the LOO-CV testing set were 0.7541 and 0.3247, respectively. Their predicted values of cytotoxicity are presented in Table 3.

The results showed that compounds (4g, 4j, 4k) with high Gu values had high cytotoxic activity against MOLT-3 cells. The analog 4k had the highest Gu value of 0.192 and was found to be the most potent compound. On the other hand, the inactive compound 4d had the lowest Gu value (0.167). It was observed that trimethoxy analog 4f had the highest Mor32u value (-0.025) while exhibiting high cytotoxicity (IC₅₀ 9.24 µM) against MOLT-3, albeit at a relatively lower level than compound 4k (IC₅₀ 1.23 µM). Recently, it has been reported that the cytotoxicity of thiopyridines against MOLT-3 showed good correlation with atomic mass descriptor, GATS4 m (Worachartcheewan et al. 2011b).

Gu is a descriptor accounting for the G total symmetry index/unweighted (González et al. 2007b; Zhang et al. 2009). This descriptor involves the information, shape and other physicochemical properties of a molecular structure. In this study, the highest Gu value was observed in compound 4k which could be attributed to an intramolecular hydrogen bonding of SO₂ group and o-OHC₆H₄ group at the C-1 position. Such interaction possibly arranges the molecule to be in a highly symmetry position as compared to the p-OH analog 4g. Mor32u and Mor31v are 3D-MoRSE (3D Molecular Representation of structures based on Electron diffraction) (Gosav et al. 2007; Habibi-Yangjeh et al. 2009) descriptors that are related to the atomic properties (e.g. atomic van der Waals volumes) to the cytotoxic effect. The QSAR studies demonstrated that trimethoxy analog 4f, which has the highest molecular weight also had the highest Mor32u value. The results suggested that the highest inhibition against MOLT-3 cells required the molecule to have high symmetry index (Gu) which would correspondingly lead to appropriate interaction with the target site of action (González et al. 2007b).

The three descriptors including PJI3 (3D Petitjean shape index), Mor32u and Mor31v (3D-MoRSE—signal 31/weighted by atomic van der Waals volumes), which

| Model | Equation | Ν | r_{Tr} | RMS_{Tr} | rcv | RMS_{CV} | R^2 | Q^2 | F value | Critical F value |
|---|---|-----------------------|--|---------------------------|----------------------------|----------------------------|-----------------------------|--------------------------|---|--------------------------------------|
| 1 | MOLT-3 $pIC_{50} = 2.0312(Mor32u) + 64.533(Gu) - 12.2097$ | 12 | 0.8899 | 0.2229 | 0.7541 | 0.3247 | 0.7919 | 0.5687 | 5.9328 | 4.2565 ^a |
| 7 | $HepG2 \ pIC_{50} = -8.9215 (PJI3) + 1.1322 (Mor32u) - 1.0483 (Mor31v) + 6.6454$ | ٢ | 0.9924 | 0.0277 | 0.9563 | 0.0726 | 0.9849 | 0.9145 | 16.0459 | 9.2766 ^b |
| <i>MOLT-3</i> set, <i>r_{Tr} c</i> square e | 3 human lymphoblastic leukemia cell line, $HepG2$ human hepatocellular carcinoma ce correlation coefficient of training set, RMS_T , root mean square error of training set, r_{CV} arror of LOO-CV testing set, R^2 square of correlation coefficient, Q^2 predictive powe | corr corr er of | e, pIC_{50} collection coefficient the model | ncentration ficient of | 1 of the cor leave-one- | mpound tha out cross va | t inhibits 5 didation (I | 50 % cell g 00-CV) ti | rrowth, <i>N</i> nu esting set, <i>R</i> | mber of the data MS_{CV} root mean |
| ^a Critici | al F value at the 95 $\%$ confidence level with 2 and 9 degrees of freedom | | | | | | | | | |

Critical F value at the 95 % confidence level with 3 and 3 degrees of freedom

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| Table 5 | The | important | descriptors | and | predicted | cytotoxic | activity |
|---------|-------|--------------------|-------------|------|-----------|-----------|----------|
| of comp | ounds | s 4a–41 aga | ainst HepG2 | cell | lines | | |

| Compound | PJI3 | Mor32u | Mor31v | Experimental activity (pIC ₅₀) | Predicted activity (pIC ₅₀) |
|----------|-------|--------|--------|--|---|
| 4a | 0.854 | -0.211 | 0.269 | >-2.157 | - |
| 4b | 0.900 | -0.305 | 0.352 | -2.094 | -2.218 |
| 4c | 0.859 | -0.171 | 0.278 | >-2.071 | - |
| 4d | 0.868 | -0.272 | 0.369 | >-2.042 | - |
| 4e | 0.866 | -0.305 | 0.227 | >-2.027 | - |
| 4f | 0.869 | -0.025 | 0.223 | -1.356 | -1.448 |
| 4g | 0.869 | -0.343 | 0.344 | -1.901 | -1.845 |
| 4h | 0.873 | -0.439 | 0.258 | -1.930 | -1.880 |
| 4i | 0.867 | -0.447 | 0.344 | -1.903 | -1.988 |
| 4j | 0.867 | -0.345 | 0.293 | >-1.998 | - |
| 4k | 0.863 | -0.265 | 0.28 | -1.650 | -1.646 |
| 41 | 0.859 | -0.226 | 0.396 | -1.694 | -1.676 |

were obtained from stepwise MLR, were important variables for predicting the cytotoxicity against HepG2 as displayed in Table 5. The descriptors used in the MLR analysis to obtain the QSAR equation (model 2) are shown in Table 4. It was observed that five compounds (4a, 4c-4e and 4j) were inactive against HepG2 cell lines, thus seven active compounds (4b, 4f-4i and 4k-4l) were used to perform the MLR. We found that the r and RMS values obtained for the training set were 0.9924 and 0.0277, respectively, while the r and RMS values for the LOO-CV testing set were 0.9563 and 0.0726, respectively. Their predicted cytotoxic activity against HepG2 is shown in Table 5.

It was found that the most potent compound 4f that inhibited HepG2 cells had the highest Mor32u value of -0.025, but had the lowest Mor31v value of 0.223. All the investigated compounds had comparably high PJI3 values (0.854–0.900), particularly, the 1-methyl analog 4b $(R = CH_3)$ had the highest PJI3 value of 0.900. In the case of compound 4a (R = H), it had the lowest PJI3 value of 0.854.

A compound with high molecular weight tends to have high hydrophobic property that enhances its cell penetration ability as in the case of compound 4f which acts as the

Table 6 Inter-correlation matrix of the three significant descriptors for predicting the pIC50 values of HepG2

| Descriptors | PJI3 | Mor32u | Mor31v |
|-------------|---------|---------|--------|
| PJI3 | 1 | | |
| Mor32u | -0.1285 | 1 | |
| Mor31v | 0.0569 | -0.3440 | 1 |



Fig. 2 Plot of the experimental and predicted anticancer activities (pIC_{50}) against MOLT-3 (a) and HepG2 (b) cell lines for the training set (*open square* regression line is represented as *dotted line*) and the

leave-one-out cross-validated testing set (filled square regression line is represented as *solid line*)

most potent cytotoxic against HepG2. On the other hand, the analog 4f had the lowest atomic van der Waals volumes (Mor31v). This could be due to the fact that the molecule had small size or volume which makes it appropriate for interacting with target cells.

To evaluate the inter-correlation of the molecular descriptors, the Pearson's correlation coefficient was calculated in SPSS. The results showed that low inter-correlation value of -0.166 were observed for descriptors from the QSAR model of MOLT-3. Descriptors from the QSAR model of HepG2 also presented low inter-correlation as displayed in Table 6. Outlier compounds were not detected when using the ± 2 standardized residual as a cutoff criteria according to Eq. (2). The performance of the QSAR model gave R^2 and Q^2 values of 0.7919 and 0.5687, respectively, for MOLT-3 and 0.9849 and 0.9145, respectively, for HepG2 (Table 4). Such values indicated that the models provided good predictive performance as the R^2 values were greater than 0.6 and the Q^2 values were higher than 0.5 (Nantasenamat et al. 2009, 2010). Plots of the experimental versus predicted activities of the compounds as anticancer agents against MOLT-3 and HepG2 cell lines are shown in Fig. 2a, b.

In conclusion, the synthesis of 1-substituted-*N*-tosyl-1,2,3,4-tetrahydroisoquinoline analogs has been accomplished by the modified Pictet–Spengler reaction of phenylethylbenzene sulfonamide with various aldehydes. Most tetrahydroisoquinoline analogs displayed cytotoxicity against MOLT-3 cell lines, in which the *o*-OH analog **4k** is the most potent compound. The trimethoxy analog **4f** is the most potent cytotoxic against HepG2 cells. QSAR studies revealed that the total symmetry index (Gu), 3D-MoRSE (Mor31v and Mor32u) and 3D Petitjean index (PJI3) were the most significant descriptors for correlating the molecular structures with their cytotoxicities. The most potent cytotoxic (4k) against MOLT-3 had the highest Gu, correspondingly the inactive compound (4d) had the lowest Gu value. On the other hand, the highest molecular mass compound (4f) was shown to be the most potent cytotoxic against HepG2 cells. The studies demonstrated that tetrahydroisoquinolines 4f and 4k are interesting potential lead pharmacophores that should be further explored. Furthermore, the obtained QSAR models are useful in the design and synthesis of novel bioactive compounds.

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