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RESEARCH ARTICLE

Synthesis, cytotoxicity and QSAR study of *N*-tosyl-1,2,3,4-tetrahydroisoquinoline 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 IC_{50} value of 1.23 μM was observed for MOLT-3 cells. Trimethoxy analog **4f** exerted the most potent activity against HepG2 with an IC_{50} of 22.70 μM, 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 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.

Keywords Cytotoxicity · Isoquinoline · Multiple linear regression · Pictet–Spengler reaction · QSAR · Sulfonamide

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 1,2,3,4-tetrahydroisoquinoline 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 sulfonyl 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-1,2,3,4-tetrahydroisoquinolines, by exploring the effects of various substituents at the C-1 position of the tetrahydroisoquinoline system. It is expected that not only the sulfonyl 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. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AVANCE 300 NMR spectrometer (operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C). 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 CH_2Cl_2 (2 × 30 mL). Combined extracts were washed with saturated aqueous $NaHCO_3$, dried (anh. Na_2SO_4) 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-[(4-methylphenyl)sulfonyl]-isoquinoline (**4a**)*

85 % yield. mp 144–145 °C [144–145 °C (Ito and Tanaka 1977)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.40 (s, 3H, $ArCH_3$), 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 × OCH_3), 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′-ArH_2), 7.69 (d, J = 8.0 Hz, 2H, C2′-ArH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{18}H_{22}NO_4S$: 348.1270).

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

89 % yield. mp: 150–151 °C [150 °C (Hazebroucq 1966)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.43 (d, J = 6.7 Hz, 3H, $CHCH_3$), 2.34 (s, 3H, $ArCH_3$), 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 × OCH_3), 5.03 (q, J = 6.7 Hz, 1H, C1), 6.42, 6.49 (2 s, 2H, C5-Ar*H*, C8-Ar*H*), 7.17 (d, J = 7.8 Hz, 2H, C3′-ArH_2), 7.64 (d, J = 7.8 Hz, 2H, C2′-ArH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{19}H_{24}NO_4S$: 362.1421).

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

92 % yield. mp: 122–123 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H, CH_3), 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 × OCH_3), 6.19 (s, 1H, C1), 6.46 (s, 2H, C5-Ar*H*, C8-Ar*H*), 7.13 (d, J = 8.0 Hz, 2H, C3″-ArH_2), 7.19–7.31 (m,

5H, C2′-ArH_2, C3′-ArH_2, C4′-Ar*H*), 7.58 (d, J = 8.2 Hz, 2H, C2″-ArH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{24}H_{26}NO_4S$: 424.1577).

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

35 % yield. mp: 119–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H, CH_3), 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 × OCH_3), 6.16 (s, 1H, C1), 6.45 (s, 2H, C5-Ar*H*, C8-Ar*H*), 6.81 (d, J = 8.0 Hz, 2H, C3″-ArH_2), 7.13 (d, J = 7.7 Hz, 4H, C2′-ArH_2, C3′-ArH_2), 7.59 (d, J = 8.2 Hz, 2H, C2″-ArH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{25}H_{28}NO_5S$: 454.1683).

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

54 % yield. mp: 171–172 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.30 (s, 3H, CH_3), 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 × OCH_3), 6.06 (s, 1H, C1), 6.39, 6.40 (2 s, 2H, C5-Ar*H*, C8-Ar*H*), 6.63–6.76 (m, 3H, C2′-Ar*H*, C5′-Ar*H*, C6′-Ar*H*), 7.07 (d, J = 8.1 Hz, 2H, C3″-ArH_2), 7.54 (d, J = 8.1 Hz, 2H, C2″-ArH_2). ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{25}H_{28}NO_6S$: 470.1632).

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

85 % yield. mp: 174–175 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.31 (s, 3H, CH_3), 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 × OCH_3), 6.05 (s, 1H, C1), 6.36, 6.42, 6.44 (3 s, 4H, C5-Ar*H*, C8-Ar*H*, C2′-ArH_2), 7.10 (d, J = 8.0 Hz, 2H, C3″-ArH_2), 7.56 (d, J = 8.2 Hz, 2H, C2″-ArH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{27}H_{32}NO_7S$: 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. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.31 (s, 3H, CH_3), 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 × OCH_3), 6.10 (s, 1H, C1), 6.39, 6.40 (2 s, 2H, C5-Ar*H*, C8-Ar*H*), 6.70 (d, J = 8.5 Hz, 2H, C3′-ArH_2), 7.02 (d, J = 8.5 Hz, 2H, C2′-ArH_2), 7.08 (d, J = 8.1 Hz, 2H, C3″-ArH_2), 7.54 (d, J = 8.1 Hz, 2H, C2″-ArH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{24}H_{26}NO_5S$: 440.1532).

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

57 % yield. mp: 125–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.35 (s, 3H, CH_3), 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 × OCH_3), 6.11 (s, 1H, C1), 6.42–6.48 (m, 3H, C5-Ar*H*, C8-Ar*H*, C6′-Ar*H*), 6.76 (d, J = 8.2 Hz, 1H, C5′-Ar*H*), 6.92 (d, J = 1.7 Hz, 2H, C2′-Ar*H*), 7.13 (d, J = 8.2 Hz, 2H, C3″-ArH_2), 7.59 (d, J = 8.2 Hz, 2H, C2″-ArH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{25}H_{28}NO_6S$: 470.1632).

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

62 % yield. mp: 148–149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.31 (s, 3H, CH_3), 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 × OCH_3), 5.48 (s, 1H, C1), 6.35 (s, 2H, C2′-ArH_2), 6.41, 6.42 (s, 2H, C5-Ar*H*, C8-Ar*H*), 7.10 (d, J = 8.2 Hz, 2H, C3″-ArH_2), 7.55 (d, J = 8.2 Hz, 2H, C2″-ArH_2). ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{26}H_{30}NO_7S$: 500.1738).

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

84 % yield. mp: 120–121 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H, CH_3), 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 × OCH_3), 6.09 (s, 1H, C1), 6.37, 6.41 (2 s, 2H, C5-Ar*H*, C8-Ar*H*), 7.06 (d, J = 8.5 Hz, 2H, C2′-ArH_2), 7.09 (d, J = 8.5 Hz, 2H, C3′-ArH_2), 7.37 (d, J = 8.0 Hz, 2H, C3″-ArH_2), 7.54 (d, J = 8.2 Hz, 2H, C2″-ArH_2). ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{24}H_{25}BrNO_4S$: 502.0682).

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

52 % yield. mp: 96–97 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 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 × OCH_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″-ArH_2), 7.20 (t, J = 7.6 Hz, 1H, C4′-ArH), 7.61 (d, J = 8.2 Hz, 2H, C2″-ArH_2). ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{24}H_{26}NO_5S$: 440.1526).

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

94 % yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.31 (s, 3H, CH_3), 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 × OCH_3), 6.17 (s, 1H, C1), 6.36, 6.44 (2 s, 2H, C5-Ar*H*, C8-Ar*H*), 7.12 (d, J = 7.9 Hz, 2H, C3″-ArH_2), 7.45–7.60 (m, 3H, C5′-Ar*H*, C2″-ArH_2), 7.97 (d, J = 7.7 Hz, 1H, Ar*H*), 8.35 (s, 1H, Ar*H*), 8.63 (d, J = 4.1 Hz, 1H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{23}H_{25}N_2O_4S$: 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–H_2O (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

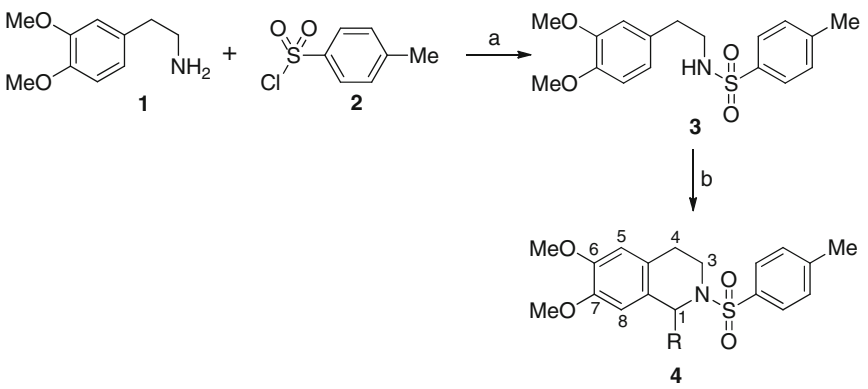
Data set

The IC_{50} (µM) values of cytotoxicity against HepG2 and MOLT-3 cell lines were converted to pIC_{50} by taking the negative logarithm to the base of 10 of the IC_{50} values. The molecular structures of the 12 compounds investigated in this study are presented in Fig. 1.

Quantum chemical and molecular descriptors calculation

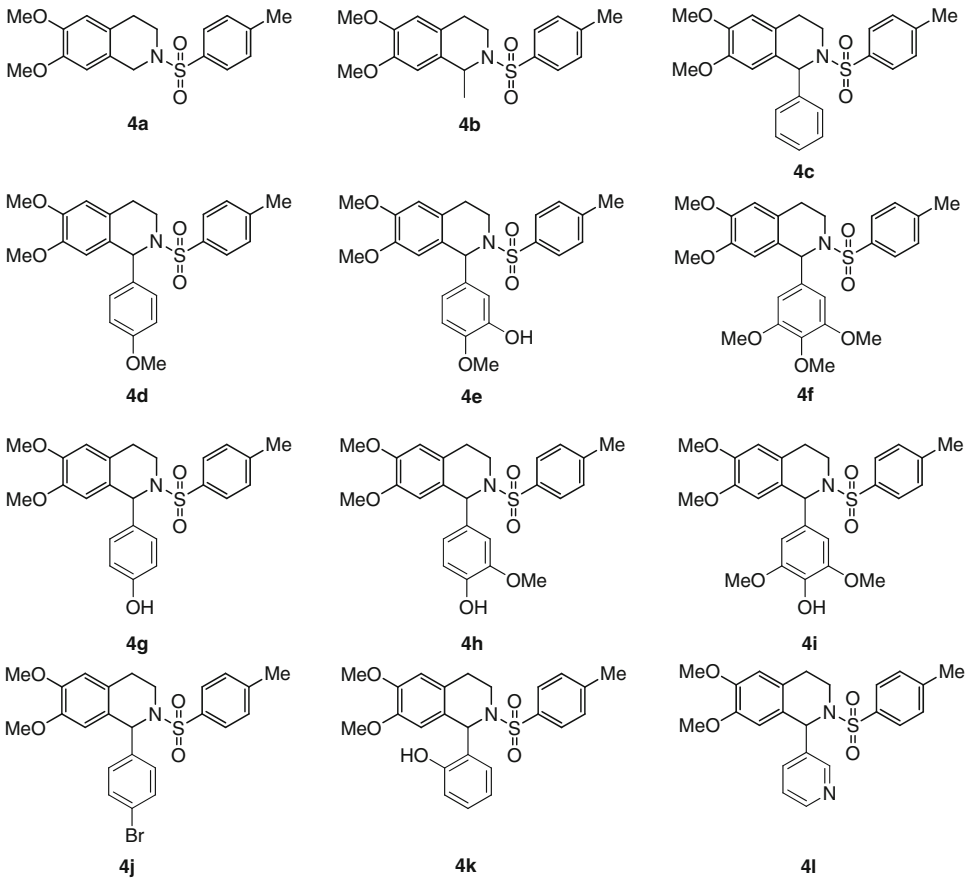
Molecular structures of the compounds were drawn using GaussView (Dennington II et al. 2003). Geometric optimization was initially performed at the semi-empirical method AM1 (Austin Model 1) and finally optimized at the DFT level using Becke's three-parameter hybrid method using the Lee–Yang–Parr correlation 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

Scheme 1 Synthesis of *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines (**4a–4l**)



Reagents and conditions: (a) Na_2CO_3, CH_2Cl_2
(b) paraformaldehyde, HCOOH, reflux for **4a**; RCHO, TFA, reflux for **4b-4l**

Fig. 1 Molecular structures of *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines (**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:

$$Y = B_0 + \sum B_n X_n \quad (1)$$

where Y is the pIC_{50} 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:

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

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, CF_3COOH). 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-1,2,3,4-tetrahydroisoquinolines 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]	**4a**	H	1	85
2	**4b**	Me	0.5	89
3	**4c**	C_6H_5	2	92
4	**4d**	4-OMe-C_6H_4	27	35
5	**4e**	3-OH,4-OMe-C_6H_3	5	54
6	**4f**	3,4,5-$(OMe)_3$-C_6H_3	12	85
7	**4g**	4-OH-C_6H_4	27	34
8	**4h**	3-OMe,4-OH-C_6H_3	5	57
9	**4i**	3,5-$(OMe)_2$,4-OH-C_6H_3	8	62
10	**4j**	4-Br-C_6H_4	2	84
11	**4k**	2-OH-C_6H_4	27	52
12	**4l**	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 ^{13}C 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 IC_{50} value of 1.23 μM against MOLT-3 cell. On the other hand, trimethoxy analog **4f** was the most potent compound (IC_{50} = 22.70 μM) 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 (CH_3) 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 **4l**. Among the tested analogs, *p*-methoxy compound (**4d**, R = *p*-$OMeC_6H_4$) was shown to be an inactive cytotoxic (IC_{50} > 110.09 μM). Remarkable cytotoxicity was found when R displayed the *p*-OHC_6H_4 (**4g**, IC_{50} = 20.06 μM) and *p*-BrC_6H_4 (**4j**, IC_{50} = 22.69 μM) substituents. However, unsubstituted phenyl analog (**4c**) exerted higher cytotoxic effect (IC_{50} 15.49 μM) 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 (IC_{50} 40.61 μM) than the parent compound **4g**. It was notable that 3,4,5-trimethoxy analog **4f** exhibited greater activity (IC_{50} 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
4l	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*-OHC_6H_4 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 near-constant 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 method to further select important descriptors using the SPSS software.

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
4l	0.179	−0.226	−1.094	−1.120

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 (IC_{50} 9.24 μM) against MOLT-3, albeit at a relatively lower level than compound **4k** (IC_{50} 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 SO_2 group and *o*-OHC_6H_4 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

Table 4 QSAR models for cytotoxic activities of 1,2,3,4-tetrahydroisoquinolines

Model	Equation	N	r_{Tr}	RMS_{Tr}	r_{CV}	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]
2	HepG2 $pIC_{50} = -8.9215(PJI3) + 1.1322(Mor32u) - 1.0483(Mor31v) + 6.6454$	7	0.9924	0.0277	0.9563	0.0726	0.9849	0.9145	16.0459	9.2766[b]

MOLT-3 human lymphoblastic leukemia cell line, *HepG2* human hepatocellular carcinoma cell line, pIC_{50} concentration of the compound that inhibits 50 % cell growth, N number of the data set, r_{Tr} correlation coefficient of training set, RMS_{Tr} root mean square error of training set, r_{CV} correlation coefficient of leave-one-out cross validation (LOO-CV) testing set, RMS_{CV} root mean square error of LOO-CV testing set, R^2 square of correlation coefficient, Q^2 predictive power of the model

[a] Critical F value at the 95 % confidence level with 2 and 9 degrees of freedom

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

Table 5 The important descriptors and predicted cytotoxic activity of compounds **4a–4l** against 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
4l	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 pIC_{50} values of HepG2

Descriptors	PJI3	Mor32u	Mor31v
PJI3	1		
Mor32u	−0.1285	1	
Mor31v	0.0569	−0.3440	1

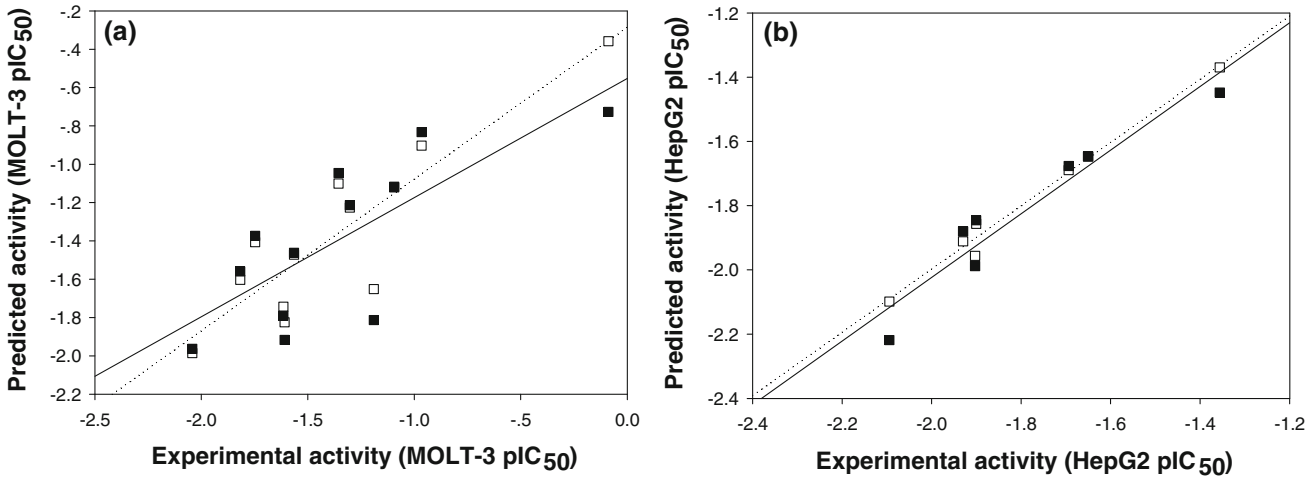


Fig. 2 Plot of the experimental and predicted anticancer activities (pIC_{50}) against MOLT-3 (**a**) and HepG2 (**b**) cell lines for the training set (*open square* regression line is represented as *dotted line*) and the leave-one-out cross-validated testing set (*filled square* regression line is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

Alves, C.N., J.C. Pinheiro, A.J. Camargo, M.M.C. Ferreira, R.A.F. Romero, and A.B.F. da Silva. 2001. A multiple linear regression and partial least squares study of flavonoid compounds with anti-HIV activity. *Journal of Molecular Structure (Theochem)* 541: 81–88.

Barn, D.R., W.L. Caulfield, J. Cottney, K. McGurk, J.R. Morphy, Z. Rankovic, and B. Roberts. 2001. Parallel synthesis and biological activity of a new class of high affinity and selective δ-opioid ligand. *Bioorganic & Medicinal Chemistry* 9: 2609–2624.

Bentley, K.W. 1998. *The isoquinoline alkaloids*. Amsterdam: Harwood Academic Publishers.

Bermejo, A., I. Andreu, F. Suvire, S. Léonce, D.H. Caignard, P. Renard, A. Pierré, R.D. Enriz, D. Cortes, and N. Cabedo. 2002. Syntheses and antitumor targeting G1 phase of the cell cycle of benzoyldihydroisoquinolines and related 1-substituted isoquinolines. *Journal of Medicinal Chemistry* 45: 5058–5068.

Bourdier, T., G. Poisnel, M. Dhilly, J. Delamare, J. Henry, D. Debruyne, and L. Barré. 2007. Synthesis and biological evaluation of *N*-substituted quinolinimides, as potential ligands for in vivo imaging studies of δ-opioid receptors. *Bioconjugate Chemistry* 18: 538–548.

Cox, E.D., and J.M. Cook. 1995. The Pictet–Spengler condensation: A new direction for an old reaction. *Chemical Reviews* 95: 1797–1842.

Cui, W., K. Iwasa, H. Tokuda, A. Kashihara, Y. Mitani, T. Hasegawa, Y. Nishiyama, M. Moriyasu, H. Nishino, M. Hanaoka, C. Mukai, and K. Takeda. 2006. Potential cancer chemopreventive activity of simple isoquinolines, 1-benzylisoquinolines, and protoberberines. *Phytochemistry* 67: 70–79.

Dennington II, R., T. Keith, J. Millam, K. Eppinnett, W.L. Hovell, and R. Gilliland. 2003. GaussView, Version 3.09. Shawnee Mission: Semichem, Inc.

Frisch, M.J., G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr, T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, and J.A. Pople. 2004. *Gaussian 03, Revision C.02*. Wallingford: Gaussian, Inc.

Gitto, R., S. Agnello, S. Ferro, L. De Luca, D. Vullo, J. Brynda, P. Mader, C.T. Supuran, and A. Chimirri. 2010. Identification of 3,4-dihydroisoquinoline-2(1H)-sulfonamide as potent carbonic anhydrase inhibitors: Synthesis, biological evaluation, and enzyme–ligand X-ray studies. *Journal of Medicinal Chemistry* 53: 2401–2408.

Gitto, R., S. Ferro, S. Agnello, L. De Luca, G. De Sarro, E. Russo, D. Vullo, C.T. Supuran, and A. Chimirri. 2009. Synthesis and evaluation of pharmacological profile of 1-aryl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-sulfonamides. *Bioorganic & Medicinal Chemistry* 17: 3659–3664.

González, J.F., E. de la Cuesta, and C. Avendaño. 2007a. Synthesis and cytotoxic activity of pyrazino[1,2-b]-isoquinolines, 1-(3-isoquinolyl)isoquinolines, and 6,15-iminoisoquino[3,2-b]-3-benzazocines. *Bioorganic & Medicinal Chemistry* 15: 112–118.

González, M.P., C. Terán, M. Teijeira, and A.M. Helguera. 2007b. QSAR studies using radial distribution function for predicting A1 adenosine receptors agonists. *Bulletin of Mathematical Biology* 69: 347–359.

Gosav, S., M. Praisler, and D.O. Dorohoi. 2007. ANN expert system screening for illicit amphetamines using molecular descriptors. *Journal of Molecular Structure* 834–836: 188–194.

Grunewald, G.L., F.A. Romero, and K.R. Criscione. 2005. 3-Hydroxymethyl-7-(*N*-substituted aminosulfonyl)-1,2,3,4-tetrahydroisoquinoline inhibitors of phenylethanolamine *N*-methyltransferase that display remarkable potency and selectivity. *Journal of Medicinal Chemistry* 48: 134–140.

Habibi-Yangjeh, A., E. Pourbasheer, and M. Danandeh-Jenagharad. 2009. Application of principal component-genetic algorithm-artificial neural network for prediction acidity constant of various nitrogen containing compounds in water. *Monatshefte fuer Chemie* 140: 15–27.

Hazebroucq, G. 1966. 2,3,4,5-Tetrahydro-1H-3-benzazepin-1-ones and hexahydroimidazoisoquinoleines. *Annales de Chimie* 1: 221–254.

Hu, L., Z.-R. Li, J.–.D. Jiang, and D.W. Boykin. 2008. Novel diaryl or heterocyclic sulfonamides as antimitotic agents. *Anti-Cancer Agents. Medicinal Chemistry* 8: 739–745.

Huszár, J., Z. Timár, K.K. Szalai, G. Keseru, F. Fülöp, and B. Penke. 2008. Novel bradykinin-1 antagonists containing a (1,2,3,4-tetrahydro-isoquinolin-1-yl)acetic acid scaffold. *European Journal of Medicinal Chemistry* 43: 1552–1558.

Ito, K., and H. Tanaka. 1977. Syntheses of 1,2,3,4-tetrahydroisoquinolines from *N*-sulfonyl-phenethylamines and aldehydes. *Chemical & Pharmaceutical Bulletin* 25: 1732–1739.

Iwasa, K., M. Moriyasu, Y. Tachibana, H.S. Kim, Y. Wataya, W. Wiegrebe, K.F. Bastow, L.M. Cosentino, M. Kozuka, and K.H. Lee. 2001. Simple isoquinoline and benzylisoquinoline alkaloids as potential antimicrobial, antimalarial, cytotoxic, and anti-HIV agents. *Bioorganic & Medicinal Chemistry* 9: 2871–2884.

Karelson, M., V.S. Lobanov, and A.R. Katritzky. 1996. Quantum-chemical descriptors in QSAR/QSPR studies. *Chemical Reviews* 96: 1027–1044.

Larghi, E.L., M. Amongero, A.B.J. Bracca, and T.S. Kaufman. 2005. The intermolecular Pictet–Spengler condensation with chiral carbonyl derivatives in the stereoselective syntheses of optically active isoquinoline and indole alkaloids. *ARKIVOC* 12: 98–153.

Lukanov, L.K., A.P. Venkov, and N.M. Mollov. 1987. Application of the intramolecular α-amidoalkylation reaction for the synthesis of 2-arylsulfonyl-1,2,3,4-tetrahydroisoquinolines. *Synthesis* 1987: 204–206.

Ma, D., W. Wu, G. Yang, J. Li, J. Li, and Q. Ye. 2004. Tetrahydroisoquinoline based sulfonamide hydroxamates as potent matrix metalloproteinase inhibitors. *Bioorganic & Medicinal Chemistry Letters* 14: 47–50.

Matter, H., M. Schudok, W. Schwab, W. Thorwart, D. Barbier, G. Billen, B. Haase, B. Neises, K.-U. Weithmann, and T. Wollmann. 2002. Tetrahydroisoquinoline-3-carboxylate based matrix-metalloproteinase inhibitors: Design, synthesis and structure–activity relationship. *Bioorganic & Medicinal Chemistry* 10: 3529–3544.

Matter, H., and W. Schwab. 1999. Affinity and selectivity of matrix metalloproteinase inhibitors: A chemometrical study from the perspective of ligands and proteins. *Journal of Medicinal Chemistry* 42: 4506–4523.

Nantasenamat, C., C. Isarankura-Na-Ayudhya, T. Naenna, and V. Prachayasittikul. 2007a. Quantitative structure-imprinting factor relationship of molecularly imprinted polymers. *Biosensors & Bioelectronics* 22: 3309–3317.

Nantasenamat, C., C. Isarankura-Na-Ayudhya, T. Naenna, and V. Prachayasittikul. 2008a. Prediction of bond dissociation enthalpy of antioxidant phenols by support vector machine. *Journal of Molecular Graphics and Modelling* 27: 188–196.

Nantasenamat, C., C. Isarankura-Na-Ayudhya, T. Naenna, and V. Prachayasittikul. 2009. A practical overview of quantitative structure–activity relationship. *EXCLI Journal* 8: 74–88.

Nantasenamat, C., C. Isarankura-Na-Ayudhya, and V. Prachayasittikul. 2010. Advances in computational methods to predict the biological activity of compounds. *Expert Opinion on Drug Discovery* 5: 633–654.

Nantasenamat, C., C. Isarankura-Na-Ayudhya, N. Tansila, T. Naenna, and V. Prachayasittikul. 2007b. Prediction of GFP spectral properties using artificial neural network. *Journal of Computational Chemistry* 8: 1275–1289.

Nantasenamat, C., T. Naenna, C. Isarankura-Na-Ayudhya, and V. Prachayasittikul. 2005. Quantitative prediction of imprinting factor of molecularly imprinted polymers by artificial neural

network. *Journal of Computer-Aided Molecular Design* 19: 509–524.

Nantasenamat, C., T. Piacham, T. Tantimongcolwat, T. Naenna, C. Isarankura-Na-Ayudhya, and V. Prachayasittikul. 2008b. QSAR model of the quorum-quenching *N*-acyl-homoserine lactone lactonase activity. *Journal of Biological Systems* 16: 279–293.

Orazi, O.O., R.A. Corral, and H. Giaccio. 1986. Synthesis of fused heterocycles: 1,2,3,4-tetrahydroisoquinoline ring homologues via sulphonamidomethylation. *Journal of the Chemical Society, Perkin Transactions* 1: 1977–1982.

Parr, R.G., R.A. Donnelly, M. Levy, and W.E. Palke. 1978. Electronegativity: The density functional viewpoint. *Journal of Chemical Physics* 68: 3801–3807.

Parr, R.G., and R.G. Pearson. 1983. Absolute hardness: Companion parameter to absolute electronegativity. *Journal of the American Chemical Society* 105: 7512–7516.

Parr, R.G., L.V. Szentpaly, and S. Liu. 1999. Electrophilicity index. *Journal of the American Chemical Society* 121: 1922–1924.

Pingaew, R., S. Prachayasittikul, S. Ruchirawat, and V. Prachayasittikul. 2013. Synthesis and cytotoxicity of novel *N*-sulfonyl-1,2,3,4-tetrahydroisoquinoline thiosemicarbazone derivatives. *Medicinal Chemistry Research* 22: 267–277.

Prachayasittikul, S., O. Wongsawatkul, A. Worachartcheewan, C. Nantasenamat, S. Ruchirawat, and V. Prachayasittikul. 2010. Elucidating the structure–activity relationships of the vasorelaxation and antioxidation properties of thionicotinic acid derivatives. *Molecules* 15: 198–214.

Saitoh, T., K. Abe, M. Ishikawa, M. Nakatani, S. Shimazu, N. Satoh, F. Yoneda, K. Taguchi, and Y. Horiguchi. 2006. Synthesis and in vitro cytotoxicity of 1,2,3,4-tetrahydroisoquinoline derivatives. *European Journal of Medicinal Chemistry* 41: 241–252.

Scott, J.D., and R.M. Williams. 2002. Chemistry and biology of the tetrahydroisoquinoline antitumor antibiotics. *Chemical Reviews* 102: 1669–1730.

Scozzafava, A., T. Owa, A. Mastrolorenzo, and C.T. Supuran. 2003. Anticancer and antiviral sulfonamides. *Current Medicinal Chemistry* 10: 925–953.

Siengalewicz, P., U. Rinner, and J. Mulzer. 2008. Recent progress in the total synthesis of naphthyridnomycin and lemonomycin tetrahydroisoquinoline antibiotics (TAAs). *Chemical Society Reviews* 37: 2676–2690.

Silveira, C.C., C.R. Bernardi, A.L. Braga, and T.S. Kaufman. 1999. Pictet–Spengler condensation of *N*-sulfonyl-β-phenethylamines with α-chloro-α-phenylselenoesters. New synthesis of 1,2,3,4-tetrahydroisoquinoline-1-carboxylates. *Tetrahedron Letters* 40: 4969–4972.

Silveira, C.C., C.R. Bernardi, A.L. Braga, and T.S. Kaufman. 2003. Thioorthoesters in the activated Pictet–Spengler cyclization. Synthesis of 1-thiosubstituted tetrahydroisoquinolines and carbon–carbon bond formation via sulfonyl iminium ions generated from N,S-sulfonyl acetals. *Tetrahedron Letters* 44: 6137–6140.

Silveira, C.C., A.S. Vieira, and T.S. Kaufman. 2006. Thiophenol-mediated improvement of the Pictet–Spengler cyclization of *N*-tosyl-β-phenethylamines with aldehydes. *Tetrahedron Letters* 47: 7545–7549.

Suksrichavalit, T., S. Prachayasittikul, C. Nantasenamat, C. Isarankura-Na-Ayudhya, and V. Prachayasittikul. 2009. Copper complexes of pyridine derivatives with superoxide scavenging and antimicrobial activities. *European Journal of Medicinal Chemistry* 44: 3259–3265.

Suvannang, N., C. Nantasenamat, C. Isarankura-Na-Ayudhya, and V. Prachayasittikul. 2011. Molecular docking of aromatase inhibitors. *Molecules* 16: 3597–3617.

Talete srl. 2007. Dragon for Windows (Software for Molecular Descriptor Calculations), version 5.5. Milano: Talete srl.

Tengchaisri, T., R. Chawengkirttikul, N. Rachaphaew, V. Reutrakul, R. Sangsuwan, and S. Sirisinha. 1998. Antitumor activity of triptolide against cholangiocarcinoma growth in vitro and in hamsters. *Cancer Letters* 133: 169–175.

Thanikaivelan, P., V. Subramanian, J. Raghava Rao, and B. Unni Nair. 2000. Application of quantum chemical descriptor in quantitative structure activity and structure property relationship. *Chemical Physics Letters* 323: 59–70.

Whitley, D.C., M.G. Ford, and D.J. Livingstone. 2000. Unsupervised forward selection: A method for eliminating redundant variables. *Journal of Chemical Information and Computer Sciences* 40: 1160–1168.

Witten, I.H., E. Frank, and M.A. Hall. 2011. *Data mining: Practical machine learning tools and techniques*, 3rd ed. San Francisco: Morgan Kaufmann.

Worachartcheewan, A., C. Nantasenamat, C. Isarankura-Na-Ayudhya, S. Prachayasittikul, and V. Prachayasittikul. 2011. Predicting the free radical scavenging activity of curcumin derivatives. *Chemometrics and Intelligent Laborary Systems* 109: 207–216.

Worachartcheewan, A., C. Nantasenamat, T. Naenna, C. Isarankura-Na-Ayudhya, and V. Prachayasittikul. 2009. Modeling the activity of furin inhibitors using artificial neural network. *European Journal of Medicinal Chemistry* 44: 1664–1673.

Worachartcheewan, A., S. Prachayasittikul, R. Pingaew, C. Nantasenamat, T. Tantimongcolwat, S. Ruchirawat, and V. Prachayasittikul. 2012. Antioxidant, cytotoxicity, and QSAR study of 1-adamantylthio derivatives of 3-picoline and phenylpyridines. *Medicinal Chemistry Research* 21: 3514–3522.

Zhang, H., Q.Y. Chen, M.L. Xiang, C.Y. Ma, Q. Huang, and S.Y. Yang. 2009. In silico prediction of mitochondrial toxicity by using GA-CG-SVM approach. *Toxicology in Vitro* 23: 134–140.