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SYNTHESIS AND IN SILICO ADMET PREDICTION OF THE PROPERTIES OF NOVEL SULFONYL INDOLE DERIVATIVES

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The article presents a method for synthesizing sulfonyl-derived indoles by rearranging the corresponding N-arylhydrazones through boiling in acetic acid saturated with dry hydrogen chloride and the addition of anhydrous zinc chloride. The ADMET resource was used to predict the pharmacokinetic indicators of absorption, distribution, metabolism, and excretion of the synthesized compounds. The study compared the predicted activity of synthesized compounds to that of active drugs containing an indole fragment, specifically indole-3-carbinol and diindolylmethane. The results indicate that the introduction of a sulfonyl group has a positive effect on the pharmacokinetic indicators of the synthesized compounds, which are comparable to those of the active drugs. Sulphonyl-derived indoles have the potential for oral administration due to their good indicators of intestinal absorption (0.009–0.097). Additionally, there is no negative effect on the central nervous system as indicated by their indicators of penetration through the blood-brain barrier (0.003–0.008). Furthermore, the compounds did not exhibit inhibition of cytochrome P450 (CYP) enzymes. Rats are potential candidates for further in vivo studies due to their low rates of mutagenicity, carcinogenicity, and acute toxicity.

Keywords: sulfonyl derivatives of indoles, Fischer reaction, N-arylhydrazones, cyclization, ADMETlab 2.0.

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Introduction

Indole is an important heterocycle [1] found in natural compounds such as tryptophan [2]. Indole derivatives demonstrate a wide range of biological activities, including antiviral [3], anti-inflammatory and analgesic [4,5], anticancer [6], antioxidant [7], anti-HIV [8], and others. Therefore, obtaining new compounds and studying their pharmacological profile is a relevant task.

Previously, we developed methods for activating C-H bonds without the use of catalysts [9,10] during our study of electrophilic rearrangements of oxazaheterocycles [11,12] and their biological activity [13]. Specifically, we developed a method for synthesizing functionalized N-aryl hydrazones from cyclohexanone-2-carboxamide [14] and obtaining indole derivatives based on them.

The aim of this study was to synthesize indole derivatives with sulfamide groups and evaluate their biological activity profile using in silico prediction.

Experimental

Unless otherwise stated, all reagents of analytical grade were purchased from commercial suppliers and used without any further purification. IR spectra were recorded on a PerkinElmer Spectrum One instrument in KBr pellets. The ^{1}H NMR spectra were obtained by using a Bruker Avance II 400 spectrometer in DMSO-d_6 and $CDCl_3$ using residual solvent peak as a reference. The mass spectra were recorded by means of a MX1321 instrument with direct injection of the sample at an ionization chamber temperature of 200^{0}C and with 70 eV ionizing electrons. Mass spectra FAB were recorded on a VG7070 instrument in fast atom bombardment mode. Desorption of atoms from a solution in *m*-nitrobenzyl alcohol was accomplished with a beam of argon atoms at 8 keV energy. Elemental analysis was performed by means of a LECO CHN-900 instrument. The reactions and the

purity of the obtained compounds were monitored by TLC on Merck Silicagel 60 F-254 plates with 10:1 $CHCl_3$–i-PrOH as eluent. Melting points were carried out using an Electrothermal 9100.

Synthesis of arylhydrazones (general method)

First, a mixture of 5 ml of water and 6 ml of concentrated hydrochloric acid was prepared. Then, 0.01 mol of the corresponding amine was dissolved in the mixture. Next, 0.69 g (0.01 mol) of dry sodium nitrite was added to the mixture with intensive stirring and cooling. In a separate container, a solution of 1.41 g (0.01 mol) of cyclohexanone-2-carboxamide in 20 ml of acetic acid was prepared. This solution was then added to the mixture of diazonium salts under stirring and cooled with ice. The reaction mixture was stirred for 15 minutes and then neutralized with a 15% NaOH solution to achieve a neutral medium. The resulting precipitate was filtered.

(E)-6-(2-(Aminosulfonyl)phenyl)hydrazono)-6-carbamoylhexanoic acid (1)

Yield 52%, yellow powder, mp 225–227^{0}C (DMF). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 11.93 (1H, s, CO_2H); 9.90 (1H, s, NH); 7.65 (2H, d, ^3J=8.7, 3,5-Ar); 7.49 (2H, d, ^3J=8.7, 2,6-Ar); 7.48 (1H, s, $CONH_2$); 6.95 (1H, s, $CONH_2$); 7.07 (2H, s, SO_2NH_2); 2.58–2.62 (2H, m, 5-CH_2); 2.21–2.24 (2H, m, 2-CH_2), 1.53–1.56 (2H, m, 4-CH_2), 1.39–1.43 (2H, m, 3-CH_2). Mas spectrum (EI), *m/z* (I_{rel}, %): 442 $[M]^+$ (66). Found, %: C 45.55; H 5.41; N 16.48. $C_{13}H_{18}N_4O_5S$. Calculated, %: C 45.61; H 5.30; N 16.36.

(Z)-6-({2-[(1,3-Thiazol-2-ylamino)sulfonyl]phenyl}hydrazono)-6-carbamoylhexanoic acid (2)

Yield 33%, light-yellow powder, mp 213–215^{0}C (DMF). IR spectrum (KBr pellets, ν, cm^{-1}): 3454 (OH); 3316 (NH); 1661 (C=O). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 9.95 (1H, s, NH); 7.61 (2H, d, ^3J=8.7, 3,5-Ar); 7.49 (1H, s, $CONH_2$); 7.45 (2H, d, ^3J=8.7, 2,6-Ar); 7.20 (1H, d, ^3J=8.7, CH); 7.00 (1H, s, $CONH_2$); 6.75 (1H, d, ^3J=8.7, CH); 2.55–2.59 (2H, m, 5-CH_2); 2.19–2.23 (2H, m, 2-CH_2); 1.50–1.53 (2H, m, 4-CH_2); 1.37–1.39 (2H, m, 3-CH_2). Mas spectrum (FAB), *m/z* (I_{rel}, %): 426 $[M+H]^+$ (100). Found, %: C 45.25; H 4.58; N 16.38. $C_{16}H_{19}N_5O_5S_2$. Calculated, %: C 45.17; H 4.50; N 16.46.

(Z)-6-[(2-{[(2,6-Dimethoxypyrimidin-4-yl)amino]sulfonyl}phenyl)hydrazono]-6-carbamoylhexanoic acid (3)

Yield 39%, yellow powder, mp 220–222^{0}C (DMF). IR spectrum (KBr pellets, ν, cm^{-1}): 3474 (OH); 3233 (NH); 1681 (C=O). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 11.78 (1H, br s, CO_2H); 10.07 (1H, s, NH); 7.74 (2H, d, ^3J=8.7, 3,5-Ar); 7.55 (1H, s, $CONH_2$); 7.52 (2H, d, ^3J=8.7, 2,6-Ar); 7.05 (1H, s, $CONH_2$); 5.94 (1H, s, CH-Py); 3.77 (6H, s, $2OCH_3$); 2.56–2.60 (2H, m, 5-CH_2); 2.19–2.23 (2H, m, 2-CH_2), 1.50–1.53 (2H, m, 4-CH_2), 1.36–1.39 (2H, m, 3-CH_2). Mas spectrum (FAB), *m/z* (I_{rel}, %): 481 $[M+H]^+$ (100). Found, %: C 47.61; H 5.13; N 17.33. $C_{19}H_{24}N_6O_7S$. Calculated, %: C 47.49; H 5.03; N 17.49.

(E)-6-[(2-{[(5-Ethyl-1,3,4-thiadiazol-2-yl)amino]sulfonyl}phenyl)hydrazono]-6-carbamoylhexanoic acid (4)

Yield 62%, orange powder, mp 210–212^{0}C (DMF). IR spectrum (KBr pellets, ν, cm^{-1}): 3461 (OH); 3279 (NH); 1643 (C=O). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 13.84 (1H, s, SO_2NH); 10.01 (1H, s, NH); 7.62 (2H, d, ^3J=8.7, 3,5-Ar); 7.53 (1H, s, $CONH_2$); 7.50 (2H, d, ^3J=8.7, 2,6-Ar); 7.04 (1H, s, $CONH_2$); 2.81–2.82 (2H, m, C<u>H</u>$_2$CH$_3$); 2.58–2.61 (2H, m, 5-CH_2); 2.21–2.24 (2H, m, 2-CH_2); 1.51–1.55 (2H, m, 4-CH_2); 1.39–1.41 (2H, m, 3-CH_2); 1.19–1.23 (3H, t, CH_2C<u>H</u>$_3$). Mas spectrum (FAB), *m/z* (I_{rel}, %): 455 $[M+H]^+$ (100). Found, %: C 44.85; H 4.76; N 18.56. $C_{17}H_{22}N_6O_5S_2$. Calculated, %: C 44.92; H 4.88; N 18.49.

(6Z)-6-({2-[(Acetylamino)sulfonyl]phenyl}hydrazono)-6-carbamoylhexanoic acid (5)

Yield 39%, white powder, mp 225–227^{0}C (DMF). IR spectrum (KBr pellets, ν, cm^{-1}): 3481 (OH); 3107 (NH_2); 3290 (NH); 1677 (C=O). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 11.8 (1H, br s, CO_2H); 10.1 (1H, s, NH); 7.62 (2H, d, ^3J=8.7, 3,5-Ar); 7.6 (1H, s, $CONH_2$); 7.54 (2H, d, ^3J=8.7, 2,6-Ar); 7.09 (1H, s, $CONH_2$); 2.54–2.56 (2H, m, 5-CH_2); 2.2 (3H, c, CH_3); 2.18–2.20 (2H, m, 2-CH_2); 1.51–1.55 (2H, m, 4-CH_2); 1.35–1.37 (2H, m, 3-CH_2). Mas spectrum (EI), *m/z* (I_{rel}, %): 384 $[M]^+$ (47). Found, %: C 46.74; H 5.39; N 14.43. $C_{15}H_{20}N_4O_6S$. Calculated, %: C 46.87; H 5.24; N 14.57.

Synthesis indoles (general methods)

In a 100 ml flask, mix 0.01 mol of arylhydrazone, 0.02 mol of $ZnCl_2$, and 30 ml of AcOH saturated with gaseous HCl (5.5 g of HCl / 100 ml of AcOH). Boil the reaction mixture in a reflux flask for 1–2 hours, then pour it onto ice and neutralize it with a 2 N K_2CO_3 solution to pH 5. Filter the precipitate and purify it by crystallization.

4-(2-Carbomoyl-5-(aminosulfonyl)-1H-indol-3-yl)butanoic acid (6)

Yield (52%), light yellow powder, mp 260–

262⁰C (DMF). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 12.16 (1H, s, CO_2H); 11.68 (1H, s, NH); 8.13 (1H, d, ^4J=2, 4-H Ar); 7.60 (1H, br s) and 7.52 (1H, br s, $CONH_2$); 7.66 (1H, dd, ^4J=2, ^3J=8.8, 6-H Ar); 7.52 (d, ^3J=8.8, 7-H Ar); 7.17 (2H, s, SO_2NH_2); 3.05 (2H, t, ^3J=7.3, CH_2); 2.26 (2H, t, ^3J=7.3, CH_2); 1.75−1.83 (2H, m, CH_2). Mas spectrum (FAB), m/z (I_{rel}, %): 326 $[M+H]^+$ (26). Found, %: C 47.80; H 4.56; N 12.81. $C_{13}H_{15}N_3O_5S$. Calculated, %: C 47.99; H 4.65; N 12.92.

4-{2-Carbomoyl-5-[(1,3-thiazol-2-ylamino)sulfonyl]-1H-indol-3-yl)}butanoic acid (7)

Yield (43%), yellow powder, mp 220−222⁰C (MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 12.02 (1H, s, CO_2H); 11.65 (1H, s, NH); 8.10 (1H, d, ^4J=2, 4-H Ar); 7.62 (1H, br s) and 7.52 (1H, br s, $CONH_2$); 7.60 (1H, dd, ^4J=2, ^3J=8.8, 6-H Ar); 7.54 (1H, d, ^3J=8.8, 6-H Ar); 7.50 (1H, d, ^3J=6.1, thiazol); 7.21 (1H, d, ^3J=6.1, thiazol); 3.06 (2H, m, CH_2); 2.26 (2H, m, CH_2); 1.80 (2H, m, CH_2); Mas spectrum (FAB), *m/z* (I_{rel}, %): 409 $[M+H]^+$ (80). Found, %: C 47.16; H 3.83; N 13.60. $C_{16}H_{16}N_4O_5S_2$. Calculated, %: C 47.05; H 3.95; N 13.72.

4-[2-Carbamoyl-5-(2,6-dimethoxypyridin-4-yl)-1H-indol-3-yl]butanoic acid (8)

Yield (38%), yellow powder, mp 253−255⁰C (DMF). ^{1}H NMR spectrum (400 MHr, $CDCl_3$), δ, ppm (*J*, Hz): 8.13 (1H, d, ^4J=2, 4-H Ar); 7.60 (1H, br s) and 7.48 (1H, br s, $CONH_2$); 7.57 (1H, dd, ^4J=2, ^3J=8.8, 6-H Ar); 7.49 (1H, d, ^3J=8.8, 6-H Ar); 6.25 (1H, s, CH Py); 3.94 (3H, s, CH_3); 3.89 (3H, s, CH_3); 3.06 (2H, m, CH_2); 2.25 (2H, m, CH_2); 1.79 (2H, m, CH_2); Mas spectrum (FAB), *m/z* (I_{rel}, %): 464 $[M+H]^+$ (90). Found, %: C 49.13; H 4.73; N 15.01. $C_{16}H_{16}N_4O_5S_2$. Calculated, %: C 49.24; H 4.57; N 15.11.

4-(2-Carbomoyl-5-{[(5-ethyl-1,3,4-thiadiazol-2-yl)amino]sulfonyl}-1H-indol-3-yl)butanoic acid (9)

Yield (52%), light-yellow powder, mp 242−245⁰C (DMF). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 11.82 (1H, s, CO_2H); 11.60 (1H, s, NH); 8.14 (1H, s, 4-H Ar); 7.62 (1H, br s) and 7.42 (1H, br s, $CONH_2$); 7.59 (1H, d, ^3J=8.8, 6-H Ar); 7.50 (1H, d, ^3J=8.8, 6-H Ar); 3.08 (2H, t, ^3J=7.3, CH_2); 2.79 (2H, q, ^3J=7.3, CH_2CH_3); 2.23−2.28 (2H, m, CH_2); 1.78−1.86 (2H, m, CH_2); 1.21 (3H, t, ^3J=7.3, CH_3). Mass spectrum (FAB), *m/z* (I_{rel}, %): 438 $[M+H]^+$ (100). Found, %: C 46.55; H 4.49; N 16.18. $C_{17}H_{19}N_5O_5S_2$. Calculated, %: C 46.67; H 4.38; N 16.01.

4-[5-[(Acetylamino)sulfonyl]-2-(aminocarbonyl)-1H-indol-3-yl]butanoic acid (10)

Yield (40%), yellow powder, mp 214−216⁰C (MeOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.10 (1H, d, ^4J=2, 4-H Ar); 7.55 (1H, br s) and 7.41 (1H, br s, $CONH_2$); 7.50 (1H, dd, ^4J=2, ^3J=8.8, 6-H Ar); 7.39 (1H, d, ^3J=8.8, 6-H Ar); 3.06 (2H, m, CH_2); 2.31 (3H, s, CH_3); 2.24 (2H, m, CH_2); 1.78 (2H, m, CH_2); Mas spectrum (FAB), *m/z* (I_{rel}, %): 368 $[M+H]^+$ (80). Found, %: C 49.16; H 4.83; N 11.58. $C_{15}H_{17}N_3O_6S$. Calculated, %: C 49.04; H 4.66; N 11.44.

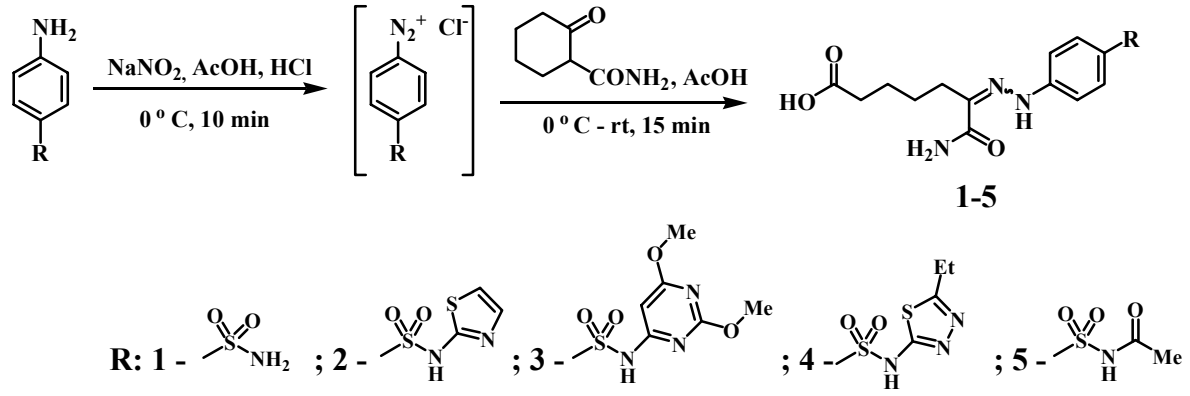
Results and discussion

Polyfunctional N-arylhydrazones with sulfamide groups were obtained by reacting cyclohexanone-2-carboxamide with diazonium salts in a mixture of hydrochloric and acetic acid (Scheme 1). The reaction on the C-sp^3 hybridized carbon atom was facilitated by the enol form of cyclohexanone-2-carboxamide in DMSO, without the need for catalysts. The structure of synthesized compounds 1−5 was determined using IR and ^{1}H NMR spectroscopy, as well as mass spectrometry.

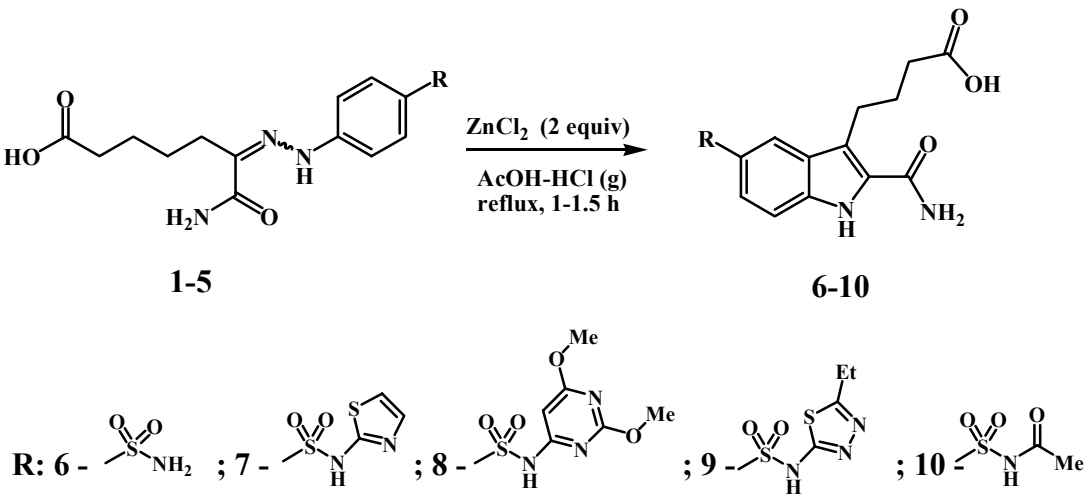
Indole derivatives containing sulfamide groups 6−10 were synthesized from arylhydrazones 1−5 using the Fischer reaction (Scheme 2). The arylhydrazones were boiled in glacial acetic acid saturated with HCl and an excess of dry zinc chloride was added for 1−1.5 hours. The structures of compounds were determined using ^{1}H NMR spectroscopy and mass spectrometry.

The ADMETlab 2.0 software resource [15] was used to evaluate the potential of indole derivatives, specifically compounds 6−10, for biological targets and predict their profile of metabolism, excretion, and toxicity. The predicted values of compounds 6−10 (Table 1) were compared to the predicted pharmacokinetic parameters of active drugs, indole-3-carbinol 11 and diindolylmethane 12 (Fig. 1). Indole 3 carbinol alters estrogen metabolism in the liver, blocks tumor cell growth and receptor activity, and increases liver enzyme activity responsible for toxin removal. Additionally, it acts as a strong antioxidant against papilloma oncovirus. Diindolylmethane promotes the formation of estrogen metabolites, supporting the health of mammary gland, intrauterine, and cervical tissues.

For further research, an ideal candidate should fall within the yellow region and outside the pink region. The studied compounds with TPSA (topological polar surface) and Log D (solubility in lipids at physiological pH 7.4) parameters that are slightly outside the defined norm are also worth considering.



Scheme 1



Scheme 2

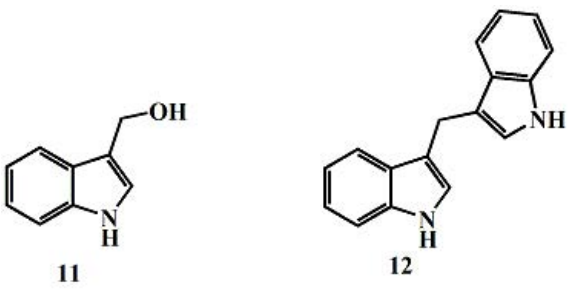


Fig. 1. Structures of indole-3-carbinol 11 and diindolylmethane 12

Table 2 presents the analysis of predicted pharmacokinetic parameters. It is widely recognized that for oral administration, a potential drug must exhibit good intestinal absorption (HIA) and penetration through the colon adenocarcinoma (Caco-2) cell lines. All studied sulfo-derivatives of indole 6–10 demonstrate excellent HIA and average Caco-2 values. Compounds 6–10 exhibit superior blood-brain barrier (BBB) penetration rates compared to compounds 11–12, making them promising candidates for further research on CNS drugs.

The potential of a drug candidate is determined by its ability to inhibit or induce cytochrome P450 (CYP) enzymes. These enzymes play a crucial role in metabolism and detoxification, so it is essential to consider the effect of the future drug on CYP450. Compounds 6–10 did not inhibit P450, indicating that they will not interfere with drugs that target these CYP enzymes.

Additionally, compounds 6–10 have a low clearance value (CL) and a short elimination half-life ($T_{1/2}$).

Table 3 presents the predicted toxicity of compounds 6–10 and drugs 11 and 12. It is important to note that, among the tested compounds 6–12, liver damage (DILI) rates are high, except for compound 11. Conversely, compounds 6–10 show very good rates of predicted mutagenicity (AMES)

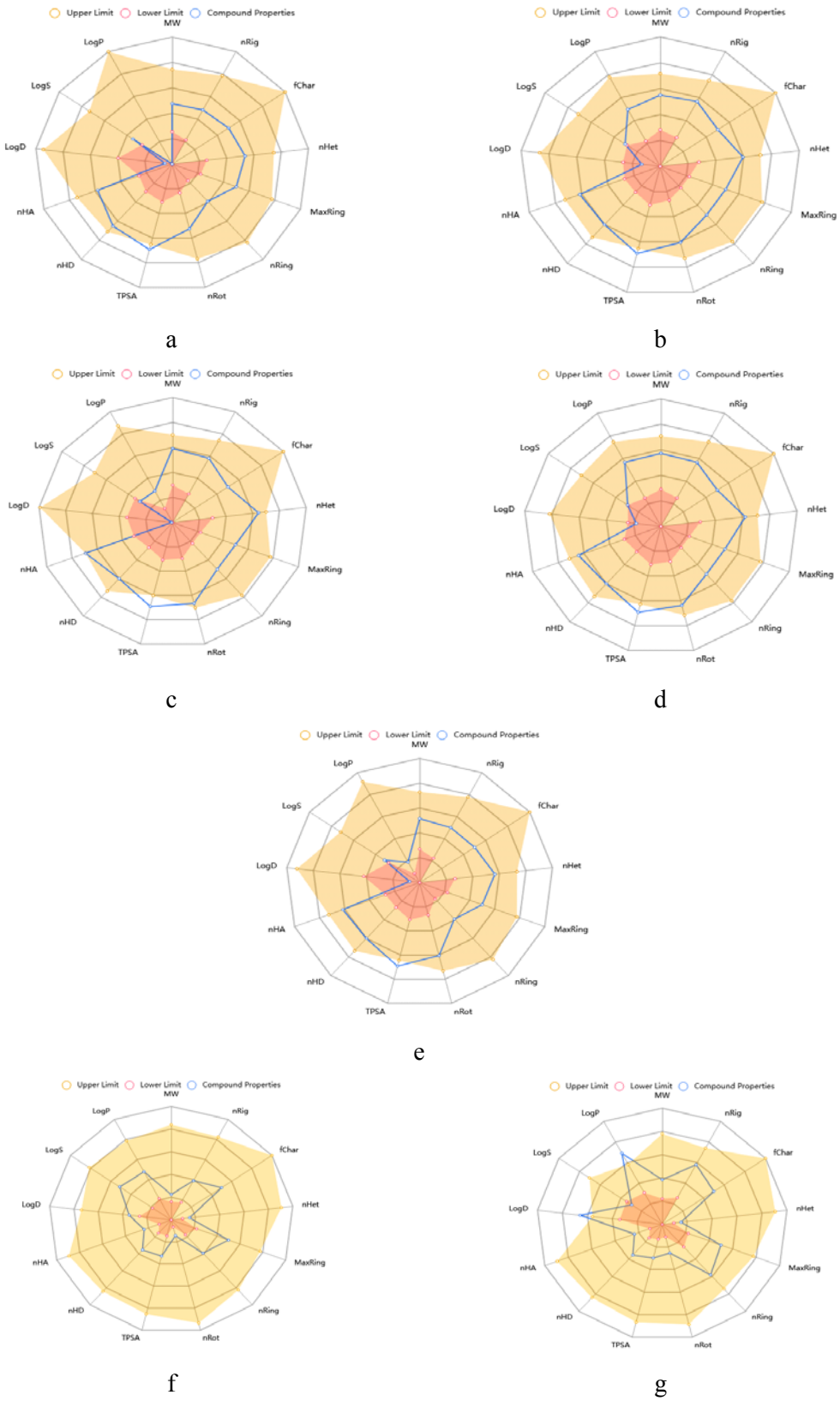


Fig. 2. Graphic representation of the analysis of the physical and chemical properties of compounds 6–12: a – 6; b – 7; c – 8; d – 9; e – 10; f – 11; and g – 12

Table 1

Determined physicochemical parameters of compounds 6–12 using ADMETlab 2.0

Compound	Normative indicators						
	MW	Log P	nHA	nHD	TPSA	nRot	Log D
	<500	<5	<10	<5	<140	<11	<3
6	325	0.001	8	6	156.34	6	–0.246
7	408	1.484	9	5	155.24	8	0.552
8	463	1.913	12	5	186.59	10	0.026
9	437	1.903	10	5	168	9	0.788
10	367	0.375	9	5	159.42	8	–0.375
11	147.07	1.39	2	2	36.02	1	1.358
12	246.12	4.18	2	2	31.58	2	3.919

Table 2

Pharmacokinetic parameters of compounds 6–12

Compound	6	7	8	9	10	11	12
Absorption (Caco-2: >–5.15: excellent; otherwise: poor/HIA: (0–0.3 excellent; 0.3–0.7 medium; 0.7–1.0 poor)							
Caco-2	–6.152	–5.997	–5.761	–5.855	–6.113	–4.411	–4.852
HIA	0.013	0.99	0.009	0.097	0.093	0.012	0.008
Distribution (0–0.3 excellent; 0.3–0.7 medium; 0.7–1.0 poor)							
BBB Penetration	0.008	0.006	0.004	0.006	0.003	0.843	0.561
Metabolism (>0.5: inhibitor/substrate; <0.5: non inhibitor/substrate)							
CYP1A2	0.01/0.03	0.02/0.11	0.02/0.44	0.03/0.09	0.07/0.09	0.95/0.77	0.97/0.61
CYP2C19	0.05/0.02	0.02/0.05	0.02/0.05	0.02/0.05	0.02/0.05	0.36/0.31	0.97/0.14
CYP2C9	0.02/0.6	0.12/0.97	0.06/0.59	0.17/0.95	0.01/0.9	0.035/0.74	0.89/0.97
CYP2D6	0.03/0.15	0.01/0.13	0.01/0.16	0.01/0.09	0.3/0.09	0.58/0.87	0.80/0.91
CYP3A4	0.02/0.05	0.03/0.18	0.02/0.21	0.02/0.11	0.01/0.08	0.08/0.21	0.93/0.24
Excretion ml/ min/kg (High: >15; Moderate: 5–15; Low: <5)							
CL	0.857	0.528	0.901	0.64	0.513	8.384	7.190
$T_{1/2}$	0.553	0.244	0.268	0.169	0.307	0.922	0.695

Table 3

Toxicological properties of compounds 6–12

Compound	Normative indicators				
	DILI	AMES	CARC	Rat Acute Toxicity	Skin Sensitization
	(0–0.3 excellent; 0.3–0.7 medium; 0.7–1.0 poor)				
6	0.99	0.009	0.271	0.035	0.025
7	0.987	0.004	0.087	0.028	0.063
8	0.992	0.003	0.044	0.028	0.02
9	0.987	0.004	0.063	0.011	0.018
10	0.984	0.006	0.023	0.001	0.039
11	0.424	0.15	0.123	0.847	0.649
12	0.917	0.609	0.044	0.202	0.782

and carcinogenicity (CARC), acute oral toxicity for rats (Rat Acute Toxicity), and skin sensitivity (Skin Sensitization). Compounds 11 and 12 are predicted to have an increased potential for skin damage. Additionally, compound 11 is predicted to have overestimated acute oral toxicity in rats.

Conclusions

We presented a successful technique for synthesizing sulfonyl-derived indoles from N-arylhydrazones through the Fischer reaction. The study analyzed the absorption, distribution, metabolism, and excretion of the synthesized compounds using in silico prediction methods with the ADME resource. The addition of a sulfonyl group to the indole ring had a beneficial impact on the pharmacokinetic parameters. The synthesized compounds predicted in this study are recommended as potential candidates for oral administration due to their low rates of mutagenicity, carcinogenicity, acute oral toxicity to rats, and skin damage. Additionally, they comply with

the rule of five. However, the predicted increased rates of liver damage suggest that further optimization of the structure of sulphonyl-derived indoles is necessary.

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СИНТЕЗ ТА IN SILICO ADMET ПРОГНОЗУВАННЯ НОВИХ СУЛЬФОНІЛПОХІДНИХ ІНДОЛІВ

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У статті описано метод синтезу сульфонілпохідних індолів перегрупуванням відповідних N-арилгідразонів при кип'ятінні в оцтовій кислоті, насиченій сухим хлороводнем з додаванням безводного хлориду цинку. За допомогою ресурсу ADMET спрогнозовано фармакокінетичні показники абсорбції, розподілення, метаболізму і виведення синтезованих сполук. Результати прогнозування синтезованих сполук порівняні з результатами прогнозування діючих лікарських препаратів, які мають індольний фрагмент, індол-3-карбінолу і дііндолілметану. За результатами прогнозування встановлено, що введення сульфонільної групи позитивно впливає на фармакокінетичні показники синтезованих сполук, які є рівними показникам діючих препаратів. Гарні показники кишкової абсорбції (0.009–0.097) сульфонілпохідних індолів робить їх потенційним кандидатом на пероральний прийом. Показники проникнення через гематоенцефалічний бар'єр (0.003–0.008) дозволяють зробити висновок про відсутність негативного впливу на центральну нервову систему. Сполуки не проявили себе інгібіторами ферментів цитохрому P450 (CYP). Низькі показники мутагенності, канцерогенності та гострої токсичності для щурів робить їх потенційними кандидатами для подальших досліджень in vivo.

Ключові слова: сульфонілпохідні індолів, реакція Фішера, N-арилгідразони, циклізація, ADMETlab 2.0.

SYNTHESIS AND IN SILICO ADMET PREDICTION OF THE PROPERTIES OF NOVEL SULFONYL INDOLE DERIVATIVES

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The article presents a method for synthesizing sulfonyl-derived indoles by rearranging the corresponding N-arylhydrazones through boiling in acetic acid saturated with dry hydrogen chloride and the addition of anhydrous zinc chloride. The ADMET resource was used to predict the pharmacokinetic indicators of absorption, distribution, metabolism, and excretion of the synthesized compounds. The study compared the predicted activity of synthesized compounds to that of active drugs containing an indole fragment, specifically indole-3-carbinol and diindolylmethane. The results indicate that the introduction of a sulfonyl group has a positive effect on the pharmacokinetic indicators of the synthesized compounds, which are comparable to those of the active drugs. Sulphonyl-derived indoles have the potential for oral administration due to their good indicators of intestinal absorption (0.009−0.097). Additionally, there is no negative effect on the central nervous system as indicated by their indicators of penetration through the blood-brain barrier (0.003−0.008). Furthermore, the compounds did not exhibit inhibition of cytochrome P450 (CYP) enzymes. Rats are potential candidates for further in vivo studies due to their low rates of mutagenicity, carcinogenicity, and acute toxicity.

Keywords: sulfonyl derivatives of indoles; Fischer reaction; N-arylhydrazones; cyclization; ADMETlab 2.0.

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