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Synthesis of 5-aryl [1,3] thiazolo[2,3-*c*] [1, 2, 4]triazol-3(2H)-one derivatives and their predictive physicochemical and Pharmacokinetic properties

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ABSTRACT

Thiazoles and triazole derivatives are well known for their biological activities and their application in the field of medicine. In this paper synthesis of fused heterobicyclic system containing thiazole and triazole has been reported. Taking 2-chloro-4-aryl-1,3-thiazole as precursor and successive reaction with hydrazine followed by reaction with ethyl chloroacetate and then cyclization step resulted in formation of thiazolotriazolone derivatives namely 5-aryl[1,3]thiazolo[2,3-*c*][1,2,4]triazol-3(2H)-one derivatives. Synthesized compounds were characterized by spectral analysis. Computational studies have been utilized to evaluate physicochemical and Pharmacokinetic (ADMET) properties using pkCSM online tool. SWISS ADME online server has been used for prediction of Physicochemical properties and Rule-based filters for Druglikeness.

Keywords: Thiazoles, triazoles, Thiazolotriazolone derivatives, physicochemical and Pharmacokinetic properties, pkCSM and SWISS ADME online server

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INTRODUCTION

Thiazoles are versatile heterocyclic compounds exhibiting pharmacological and biological activities. **[1,2]**. Any heterocyc1ic moiety either linked to or fused with thiazoles is considered to improve the bioactivity of such system(s). Drugs having Triazole derivative are well known as antibiotic **[3]**, antifungal **[4,5,6]**, antiviral **[7]**, antitumor **[8]**,and anti-epileptic **[9]** agents. Triazoles are also used as agrochemicals **[10]**. Keeping this in view, it was of interest to synthesize fused heterobicyclic molecules containing thiazole as well as triazole moiety.

In present study,2-bromo-1-arylethan-1-one (**1a-1c**) were used to prepare benzoyl thiocyanates (**2a-2c**) by reaction with potassium thiocyanate. Passing HCl gas through benzoyl thiocyanates resulted in formation of 2-chloro-4-aryl-1,3-thiazoles (**3a-3c**). The reaction of 2-chloro-4-aryl-1,3-thiazoles with hydrazine hydrate gave 2-hydrazinyl-4-aryl-1,3-thiazoles (**4a-4c**). These 2-hydrazinyl-4-aryl-1,3-thiazoles were treated with ethylchloroformate to yield ethyl-2-(4-aryl-1,3-thiazol-2-yl)hydrazine-1-carboxylate (**5a-5c**), which on cyclization gave 5-aryl[1,3]thiazolo[2,3-*c*][1,2,4]triazol-3(2H)-one derivatives (**6a-6c**).

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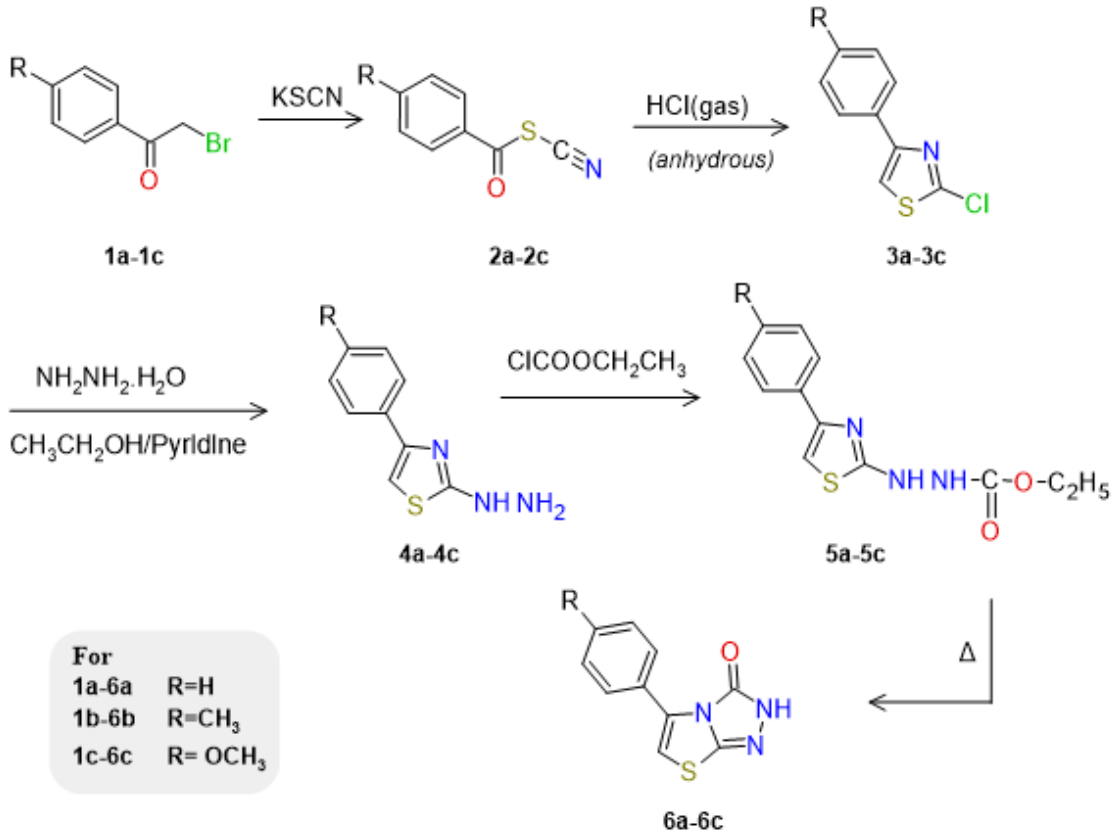
The synthetic strategy has been summarized in **Scheme 1**.



Scheme 1: Synthesis of 5-aryl[1,3]thiazolo[2,3-*c*][1,2,4]triazol-3(2*H*)-one (**6a-6c**)

EXPERIMENTAL

The starting materials and reagents were used as obtained from commercial suppliers. The solvents were purified in compliance with normal pre-use procedures. The 1H NMR spectra were recorded on Perkin Elmer R-32 (90 MHz) and Jeol FX 200 MHz NMR instrument using TMS as internal standard and DMSO-d6/$CDCl_3$ as solvent.

Chemical shifts are given in parts per million (δ-scale) and coupling constants are given in Hertz. The IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer. Elemental analysis (C, H and N) was taken with Heraeus CHN-rapid analyser and the data showed good agreement between the experimentally determined values and the theoretically calculated values.

Synthesis of benzoyl thiocyanates (2a-2c) [11]

Benzoyl thiocyanate (**2a**; *General Procedure*): 2-bromo-1-phenylethan-1-one **1a** (2.0g) was dissolved in ethanol (15 ml). To this, hot aqueous solution of potassium thiocyanate (1.9 g) was added with stirring. The mixture after heating at 50-60ºC for 10 minutes, was left at room temperature for four hours. The mixture was

poured into ice. The solid separated was filtered, washed with water and dried to obtain benzoyl thiocyanate **2a** (1.4g). The product was used as such without crystallization.

4-Methylbenzoyl thiocyanate (**2b**)**:** The reaction of **1b** (2.0 g) with potassium thiocyanate (0.92 g) yielded the product **2b** (1.25 g) as yellow solid**.**

4-Methoxybenzoyl thiocyanate (**2c**)**:** The reaction of **1c** (2.0 g) with potassium thiocyanate (0.85 g) gave **2c** (1.20 g).

Synthesis of 2-chloro-4-aryl-1,3-thiazoles (3a-3c) [11]

2-Chloro-4-phenyl-1,3-thiazole (**3a**; *General procedure*): A solution of benzoyl thiocyanate **2a** (3.0 g) in ether, was cooled to 10º C and saturated with dry HCl gas for 2-2½ hours. During the passage of HCl gas, a clear solution was formed, followed by the precipitation of 2-Chloro-4-phenyl-1,3-thiazole **3a**. The solid was filtered and washed with water to obtain white crystalline **3a**. Yield (69 %, 2.5 g); m.p. 50-51ºC, Lit m.p. 50-51ºC.

2-Ch1oro-4-(4-methy1pheny1)-1,3- thiazole (**3b**): The dry HCl gas was passed through solution of **2b** (3.0 g) in ether, to obtain **3b.** Yield (70 %, 2.5 g); m.p. 80º-81ºC, Lit m.p. 82º-83ºC.

2-Ch1oro-4-(4-methoxyphenyl)-1,3- thiazole (**3c**): The dry HCl gas was passed through solution of **2c** (3.0 g) in ether, to obtain **3c;** Yield (66 %, 2.3 g); m.p. 94º-96ºC, Lit m.p. 96º-97ºC**.**

Synthesis of 2-hydrazinyl-4-aryl-1,3-thiazoles (4a-4c) [12]

2-Hydrazinyl-4-phenyl-1,3-thiazole (**4a**; *General procedure*): The 2-Chloro-4-phenyl-1,3-thiazole **3a** (1.0g) and hydrazine hydrate (5.0 mL) in ethanol (20 mL), in presence of pyridine (0.2 mL) were refluxed for 30-45 minutes. The solvent was distilled off and the mixture was poured into ice. The pyridine was neutralized with dilute HCl. The solid obtained was filtered, washed with water and dried. The product 2-hydrazinyl-4-phenyl-1,3-thiazole **4a** (0.7 g) was obtained as off-white crystals. Yield (72 %, 0.7 g); m.p.161-163ºC, Lit m.p. 163ºC

2-Hydrazinyl-4-(4-methy1phenyl)-1,3- thiazole (**4b**) **:** The condensation of **3b** (1.0 g) with hydrazine hydrate (5mL) gave the product **4b**; Yield (62 %, 0.6 g); m.p.174-175ºC, Lit m.p.174-175ºC.

2-Hydrazinyl-4-(4-methoxypheny)-1,3- thiazole (4c) : The condensation of **3c** (1.0 g) with hydrazine hydrate (5mL) gave the product **4c**. Yield (61 %, 0.6 g); m.p. 170º-172ºC, Lit m.p. 174ºC.

Synthesis of Ethyl-2-(4-aryl-1,3-thiazol-2-yl) hydrazine-1-carboxylate (5a-5c)

Ethyl-2-(4-phenyl-1,3-thiazol-2-yl)hydrazine-1-carboxylate (**5a**; *General Procedure*): A mixture of 2-hydrazinyl-4-phenyl-1,3-thiazole **4a** (0.5 g) and ethylchloroformate (0.29 mL) was refluxed in pyridine (10 mL) for 20 minutes. The mixture was treated with cold dilute HCl solution. The solid obtained was filtered, washed with water and dried. The product ethyl-2-(4-phenyl-1,3-thiazol-2-yl)hydrazine-1-carboxylate **5a** was obtained as yellow crystalline solid. Yield (65 %, 0.44 g); m.p. 175-176ºC;1H NMR ($CDCl_3$) δ: 1.30 (t, 3H, $OCH_2C\boldsymbol{H_3}$), 4.20 (q, 2H, $OC\boldsymbol{H_2}CH_3$), 6.85 (s, 1H, H-5), 7.50 (m, 3H, Ar-H); 7.81 (m, 2H, ArH); IR (υ cm^{-1} nujol): 3200 (-

NH), 1750 (>C=O); Elemental analysis: C (54.70%) H (5.01%) N(15.89%) ;$C_{12}H_{13}N_3O_2S$;Formula Weight: 263.31, requires ;C(54.74%) H(4.98%) N(15.96%)

Ethyl-2-[(4-(4-methylphenyl)-1,3-thiazol-2-yl]hydrazine-1-carboxylate (**5b**):A mixture of **4b** (0.5 g) and ethylchloroformate (0.35 mL) on refluxing in pyridine yielded **5b** .Yield (45 %, 0.3g); m.p. 224-254ºC ; 1H NMR ($CDCl_3$) δ: 1.30 (t, 3, $OCH_2C\boldsymbol{H_3}$), 2.20 (S, 3H, CH_3), 4.21(q,2H, $OC\boldsymbol{H_2}CH_3$), 6.75 (s, 1H, H-5), 7.21 (d, J=9 Hz, 2H, Ar-H) 7.55 (J=9Hz, 2H, ArH);IR (υ cm^{-1} nujol): 3200 (-NH), 1745 (>C=O); Elemental analysis: Found C 56.20 , H 5.59 %, N 15.11%; $C_{13}H_{15}N_3O_2S$, Formula Weight: 277.34; requires;: C(56.30%) H(5.45%) N(15.15%).

Ethyl-2-[(4-(4-methoxyphenyl)-1,3-thiazol-2-yl]hydrazine-1-carboxylate (5c): Reaction of **4c** (0.5 g) and ethy1chloroformate (0.4 mL) gave **5c** as an oil. Yield (45 %,0.3 g). Elemental analysis: C(53.23%) H(5.15%) N(14.32%) O(16.36%) S(10.93%); $C_{13}H_{15}N_3O_3S$, Formula Weight: 293.34, requires: C(53.23%) H(5.15%) N(14.32%)

Synthesis of 5-aryl[1,3]thiazolo[2,3-*c*][1, 2, 4]triazol-3(2H)-one (6a-6c)

5-pheny1thiazolo[2,3-*c*][1, 2, 4]triazol-3(2H)-one (**6a**; *General Procedure*): Heating **5a** (0.5g)in an oil bath, above its melting point (30°-40 C higher), for 30-45 minutes yielded a solid which was triturated with methanol to obtain 5-phenyl-1,3-thiazolo[2,3-*c*][1, 2, 4]triazol-3(2H)-one **6a**. Yield (73 %, 0.3 g); m.p. 205-206º C. 1H NMR (DMSO-d6) δ: 7.1-7.6 (m, Ar-H and H-6).IR (υ cm^{-1} nujol): 3280-3400 (-NH), 1630-1670(>C=O) , 1600 (C=N),Elemental analysis: Found C 56.31, H 3.53, N 18.81 %; $C_{10}H_7N_3OS$; Formula Weight: 217.24,requires; C(55.29%) H(3.25%) N(19.34%)

5-(4-methylphenyl) [1,3]thiazolo[2,3-*c*][1, 2, 4]triazol-3(2H)-one (**6b**): Heating **5b** in an oil bath, above its melting point, resulted in its cyclization and **6b** was obtained. Yield (61 %, 0.25 g); m.p. 260-262ºC;1H NMR (DMSO-d6) δ: 2.1 (s, 3H, $C\boldsymbol{H_3}$), 3.3 (s, 1H, changeable), 7.2-7.6 (m, 5H, Ar-H and H-6);IR (υ cm^{-1} nujol): 3280-3400 (-NH), 1680 (>C=O), 1600 (C=N) ;Elemental analysis: Found 56.81, H 3.21, N 18.43% ; $C_{11}H_9N_3OS$; Formula Weight: 231.27 ,requires C(57.13%) H(3.92%) N(18.17%).

5-(4-methoxyphenyl)[1,3]thiazolo[2,3-*c*][1, 2, 4]triazol-3(2H)-one (**6c**) :Heating **5c** resulted in cyclization and **6c** was obtained as thick oil **.** Yield (60 %, 0.25 g); 1H NMR (DMSO-d6) δ: Insoluble in deuterated solvents.IR (υ cm^{-1} nujol): 3300 (-NH), 1670 (>C=O), 1590 (C=N) Elemental analysis: Found C 52.10, H 3.22, N 16.81 %; $C_{11}H_9N_30_2S$, Formula Weight: 247.27 requires C (53.43%) H (3.67%) N (16.99%).

RESULT AND DISCUSSION

Cyclization of Ethyl-2-(4-aryl-1,3-thiazol-2-yl)hydrazine-1-carboxylate **5a-5c**, gave 5-aryl[1,3]thiazolo[2,3-*c*] [1, 2, 4] triazol-3(2H)-one **6a-6c**. The mechanism of cyclization is depicted in **Scheme 2**. Tautomerisation in **5a** occurs where hydrogen from hydrazine Nitrogen is replaced to nitrogen of thiazole ring. The nucleophilic attack of nitrogen (of thiazole ring) on electrophilic carbonyl carbon forms a 5-membered cyclic system. Ethoxide ion acts as a leaving group, resulting in the formation of 5-phenyl[1,3]thiazolo[2,3-*c*][1,2,4]triazol-3(2H)-one **6a**. The formation of **6a** is indicated by absence of signals for OCH_2CH_3 in the 1H NMR of **6a**. Synthesized compounds were characterized by spectral and elemental analysis.

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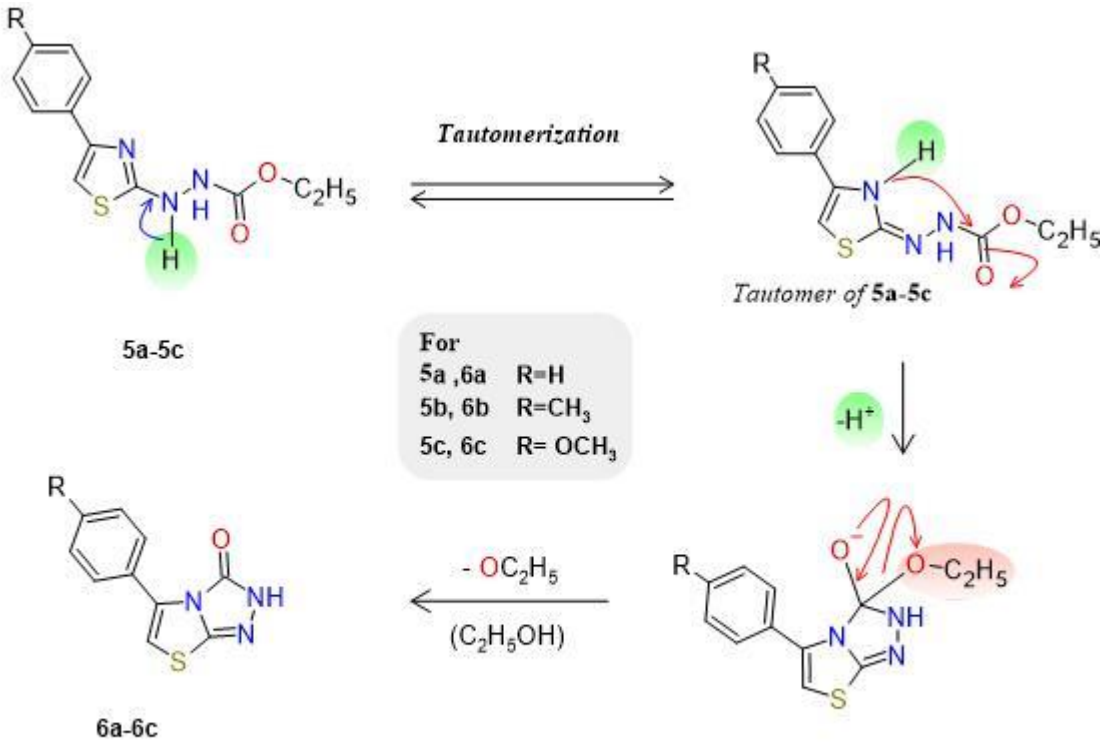

Scheme 2: Proposed mechanism for cyclization of **5a-5c** for the formation of 5-aryl[1,3]thiazolo[2,3-*c*][1,2,4]triazol-3(2*H*)-one (**6a-6c**)

ADMET properties and Drug-likeness

Physicochemical and Pharmacokinetic properties (ADMET) of 5-aryl[1,3]thiazolo[2,3-*c*][1, 2, 4]triazol-3(2H)-one (**6a-6c**) are predicted with pkCSM online tool **[13].** Pharmacokinetic properties (ADME) and Toxicity profile of **6a-6c**, has been summarized in **Table 1** and **Table 2** respectively.

Further SWISS ADME online server **[14]** has been used for prediction of Physicochemical properties and Rule-based filters for Drug-likeness for 5-aryl[1,3]thiazolo[2,3-*c*][1, 2, 4]triazol-3(2H)-one (**6a-6c**) and the outcome is given in **Table 3.**

ADMET Properties

The parameter logS are used to evaluate aqueous solubility. All three compounds show considerable solubility in water. Compounds show high (> 0.9) Caco-2 permeability and good absorption. Intestinal absorption of all three compounds in the range of 93%-94% indicates very good absorption through the human intestine. The logKp values (> -2.5) predict low skin permeability. The steady state volume of distribution (VDss) in the range <-0.15is a low value which means lesser distribution in tissues.

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Table 1. Pharmacokinetic properties (ADME) of 5-aryl[1,3]thiazolo[2,3-*c*][1, 2, 4]triazol-3(2H)-one derivatives (**6a-6c**) with pkCSM online tool

Properties	Compounds			Unit
	6a (R=H)	**6b ($R=CH_3$)**	**6c ($R=OCH_3$)**	
Absorption				
• Water solubility	-3.044	-3.11	-2.832	Numeric (log mol/L)
• Caco-2 permeability	1.258	1.258	1.232	Numeric (logPapp in 10^{-6} cm/s)
• Intestinal absorption (human)	93.436	93.631	94.535	Numeric (% Absorbed)
• Skin permeability	-2.772	-2.786	-2.81	Numeric (log Kp)
Distribution				
• VDss (human)	-0.368	-0.287	-0.143	Numeric (log L/kg)
• BBB permeability	0.356	0.345	0.055	Numeric (log BB)
• CNS permeability	-3.589	-3.565	-3.649	Numeric (log PS)
Metabolism				
• CYP2D6 substrate	Yes	Yes	Yes	Categorical (Yes/No)
• CYP1A2 inhibitior	Yes	Yes	Yes	Categorical (Yes/No)
Excretion				
• Total clearance	0.254	0.192	0.162	Numeric (log mL/min/kg)

The Blood Brain Barrier (BBB) protects brain from exogenous compounds. These compounds cannot readily cross the Blood Brain Barrier. The blood brain permeability-surface area product log PS is a direct method for measuring the blood brain permeability. Since compounds have log PS< -3, these are unable to penetrate the CNS. The cytochrome P450 is responsible for metabolism of many drugs. The two main isoforms responsible for drug metabolism are 2D6 and 3A4.All three compounds are likely to be CYP2D6 substrate and so will be metabolized by P450. All are CYP1A2 inhibitor and would not allow the metabolism of xenobiotics in the body. Metabolic activities not indicated for CYP3A4 substrate, CYP2C19 inhibitior, CYP2C9 inhibitior, CYP2D6 inhibitior and CYP3A4 inhibitior. The rate of drug elimination divided by its plasma concentration is expressed as Total clearance. A low value (< 0.477) of Total clearance indicate that these compounds will not be eliminated from the body. Compounds **6a** and **6c** are AMES positive, while **6b** is AMES negative. AMES positive molecules are mutagenic and may act as carcinogen. Molecules are not hERG I and II inhibitor and are not cardiotoxic. None of the molecules showed hepatotoxicity and skin sensitization. These were found to be non-toxic towards Minnow fish, however *T. pyriformis* toxicity value is > - 0.5 for these molecules which may be considered Toxic.

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Table 2. Toxicity profile of 5-aryl[1,3]thiazolo[2,3-*c*][1, 2, 4]triazol-3(2H)-one derivatives (**6a-6c**) with pkCSM online tool

Properties	Compounds			Unit
	6a (R=H)	**6b ($R=CH_3$)**	**6c ($R=OCH_3$)**	
AMES toxicity	Yes	No	Yes	Categorical (Yes/No)
Max. tolerated dose (human)	0.239	0.238	0.26	Numeric (log mg/kg/day)
hERG I & II inhibitor	No	No	No	Categorical (Yes/No)
Oral Rat Acute Toxicity (LD50)	2.825	2.829	2.757	Numeric (mol/kg)
Oral Rat Chronic Toxicity (LOAEL)	1.428	1.308	1.414	Numeric (log mg/kgbw/day)
Hepatotoxicity	No	No	No	Categorical (Yes/No)
Skin Sensitization	No	No	No	Categorical (Yes/No)
T. Pyriformis toxicity	0.362	0.376	0.361	Numeric (log ug/L)
Minnow toxicity	1.136	1.049	0.964	Numeric (log mM)

Molecular properties and drug-likeness

The Physicochemical properties and drug-likeness of synthesized compounds are predicted using Swiss ADME. Physicochemical prediction consisting of molecular weight (BM), number of hydrogen bond donor (HBD), number of hydrogen bond acceptor (HBA), number of rotatable bonds (Torsion), carbon bond saturation (Fsp3), topological polar surface area (TPSA), oil to water partition coefficient (log P), and solubility (logS) were evaluated.

Table 3. Physicochemical properties and Rule-based filters for Drug likeness of 5-aryl [1,3] thiazolo [2,3-*c*] [1,2,4] triazol-3(2H)-one (**6a-6c**) predicted from SWISS ADME online

Properties	Compounds 5-aryl [1,3] thiazolo[2,3-*c*] [1, 2, 4]triazol-3(2H)-one		
	6a (R=H)	**6b ($R=CH_3$)**	**6c ($R=OCH_3$)**
• Molecular weight (g/mol)	217.25	231.27	247.27
• No. of heavy atoms	15	16	17
• No. of arom. heavy atoms	14	14	14
• Fraction Csp^3	0.00	0.03	0.09
• No. of rotatable bonds	1	1	2
• No. of H-Bond acceptors	2	2	3

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Table 3 *cont.*

• No. of H-Bond donors	1	1	1
• Molar refractivity	59.13	64.09	65.62
• Total polar surface area Å²	78.40	78.40	87.63
Solubility			
• log S (ESOL)	-2.90	-3.18	-2.92
• log S (Ali)	-2.99	-3.38	-3.16
• log S (SILICOS-IT)	-3.41	-3.80	-3.54
Lipophilicity			
• Consensus logP	1.99	2.33	1.98
Skin Permeation			
• logKp cm/s^{-1}	-6.40	-6.22	-6.60
Drug likeness	**Yes**	**Yes**	**Yes**
• Lipinski violations	0	0	0
• Ghose violations	0	0	0
• Veber violations	0	0	0
• Egan violations	0	0	0
• Muegge violations	0	0	0
• Bioavailability score	0.55	0.55	0.55
• PAINS No. of alerts	0	0	0
• Brenk No. of alerts	0	0	0
• Lead-likeness: No. of violations	1(MW <250)	1(MW <250)	1(MW <250)
Synthetic accessibility Score	2.76	2.86	2.77

The bioavailability radar and BOILED -Egg prediction for compounds has been given in **Figure 1**.

Points located in the BOILED -Egg's white are compounds predicted to be passively absorbed by the gastrointestinal tract.Red dots are for molecules predicted not to be effluated from the central nervous system by the P-glycoprotein. To be estimated as druglike the red line of the compound under study must be fully included in the pink area. Any deviation represents a suboptimal physicochemical property for oral bioavailability.

The molecules appeared to have good drug likeness with zero violations as per the standards defined by Lipinski, Ghose, Veber,Egan and Muegge filter.

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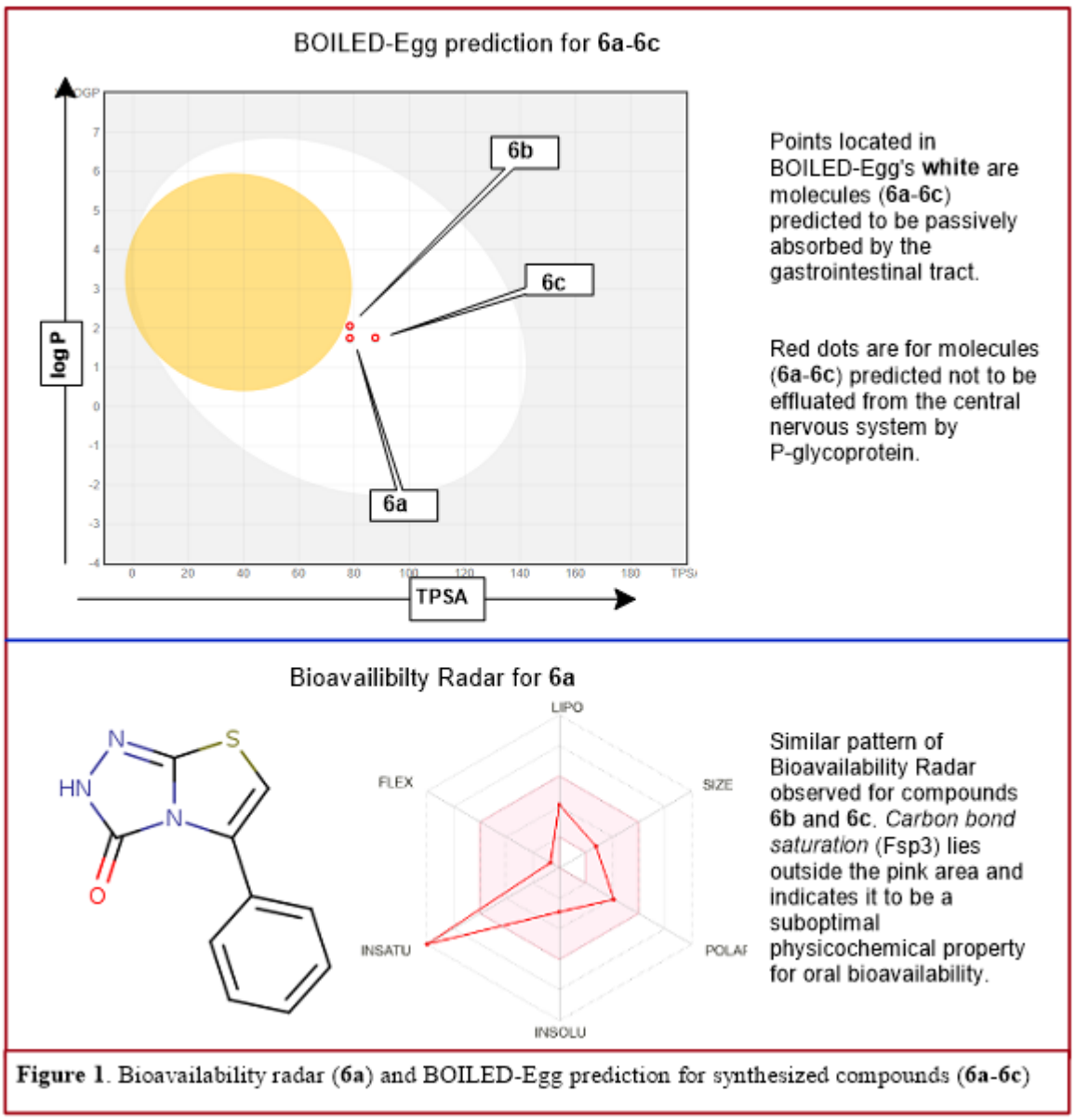

Figure 1. Bioavailability radar (**6a**) and BOILED-Egg prediction for synthesized compounds (**6a-6c**)

CONCLUSION

Synthesis of 5-aryl[1,3]thiazolo[2,3-*c*][1,2,4]triazol-3(2H)-one derivatives(**6a-6c**) was carried out taking 2-chloro-4-aryl-1,3-thiazoles (**4a-4c**) as precursor. Synthesized compounds were characterized by spectral and elemental analysis. Physicochemical, Pharmacokinetic properties and toxicity profile (ADMET) of 5-aryl[1,3]thiazolo[2,3-*c*][1,2,4]triazol-3(2H)-one (**6a-6c**) are predicted with pkCSM online tool. Compounds show high Caco-2 permeability and good absorption through the human intestine. The logKp values predict low skin permeability. Compounds are unable to penetrate the CNS. All three molecules are likely to be CYP2D6 substrate and so will be metabolized by P450. Total clearance values indicate that these molecules will not be eliminated from the body. Compounds **6a** and **6c** are AMES positive and may act as carcinogen., while **6b** is AMES negative. Compounds are not cardiotoxic. None of the molecules showed hepatotoxicity and skin sensitization. The SWISS(ADME) prediction indicates all compounds to have good drug likeness with zero violations as per the standards defined by Lipinski, Ghose, Veber,Egan and Muegge filter.

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