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Synthesis of 1-(4-Aryl-1, 3-thiazol-2-yl)-1, 2-diazinane-3, 6-dione derivatives and their predictive physicochemical properties

Manju Mehta

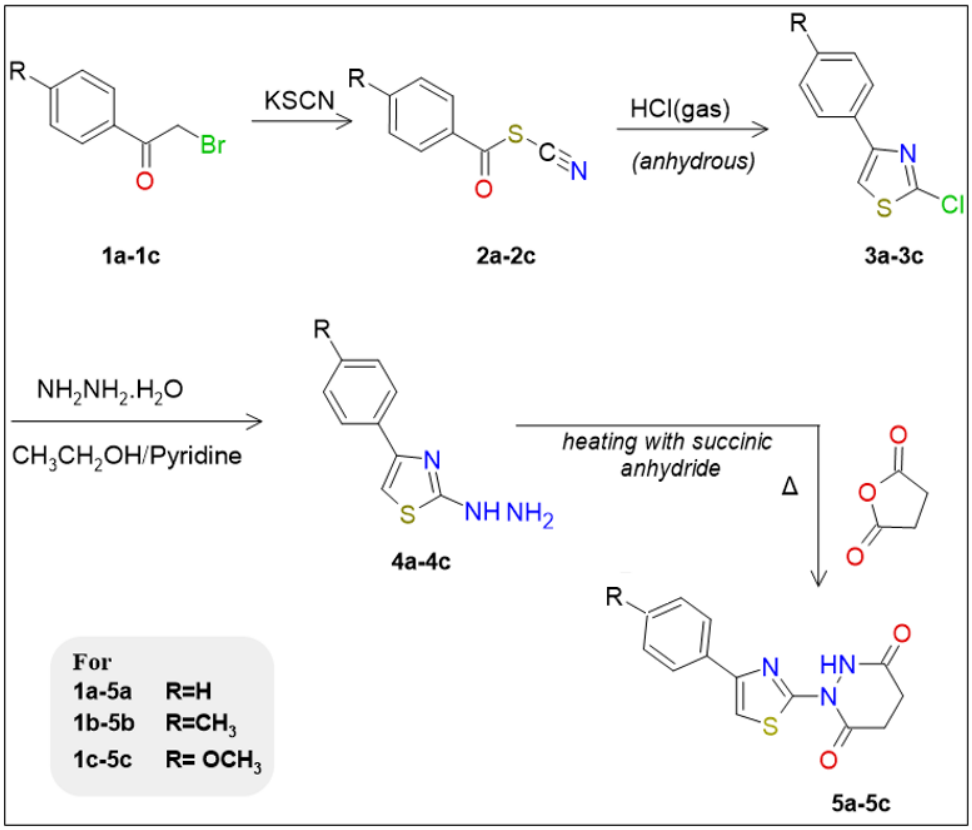
Abstract
Thiazoles and pyridazine derivatives belong to most versatile and active class of heterocyclic compounds. These have attracted special attention due to their immense biological, pharmacological, and agricultural activities. In the present communication, synthesis of 1-(4-aryl-1, 3-thiazol-2-y1)-1, 2-diazinane-3, 6-diones has been carried out by reaction of 2-hydrazinyl-4-aryl-1, 3-thiazole with succinic anhydride. The synthesized compounds were characterized by spectral analysis. Also, predictive evaluation of their Physicochemical properties, like logP, logD, logS (Intrinsic solubility), pKa (acidic and basic), microspecies distribution at different pH and HLB (hydrophilic-lipophilic balance), was carried out with Chem Axon chemicalize online server.

Keywords: thiazolyl-1, 2- diazinane-3, 6- dione derivatives, acidic and basic pKa, microspecies, logP, logD, logS (Intrinsic solubility)

Introduction
Heterocyc1ic compounds are associated with diverse pharmacological and biological activities [1]. This wide field of heterocyclic compounds includes thiazoles, imidazoles, triazoles, diazines, pyridazines, fused heterocyclic moieties etc. Thiazoles are versatile substrates that are important part of a number of drugs [2].
Pyridazines [3, 4] are well known for their medicinal importance [5] as these exhibits antibacterial, antipyretic, anticonvulsant, antifungal, antitubercular, analgesic, antidiabetic, anti-cancer, and other biological properties [6-11]. Pyridazines are also used as agrochemicals [12]. Keeping this in view, it was of interest to synthesize heterobicyclic molecules where Thiazole and hydropyridazine (diazinane) moieties are joined together, as such system is expected to have improved bioactivity.The present paper describes the synthesis of some 1-(4-aryl-1, 3-thiazol-2-yl)-1, 2-diazinane-3, 6-dione 5a-5c and different steps of the reaction sequence has been summarized in Scheme 1.

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) [13]
Benzoyl thiocyanate (**2a**; *General Procedure*): 2-bromo-1-phenylethan-1-one 1a (2.0 g) 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 50-60 ºC 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.



Scheme 1: Synthesis of 1-(4-aryl-1, 3-thiazol-2-yl)-1, 2-diazinane-3, 6-dione 5a-5c

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) [13]

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. 50-51 ºC, Lit m.p. 50-51 ºC.

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-81 ºC, Lit m.p. 82º-83 ºC.

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-96 ºC, Lit m.p. 96º-97 ºC.

Synthesis of 2-hydrazinyl-4-aryl-1, 3-thiazoles (4a-4c) [14]

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.161-163 ºC, Lit m.p. 163 ºC.

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

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-172 ºC, Lit m.p. 174 ºC.

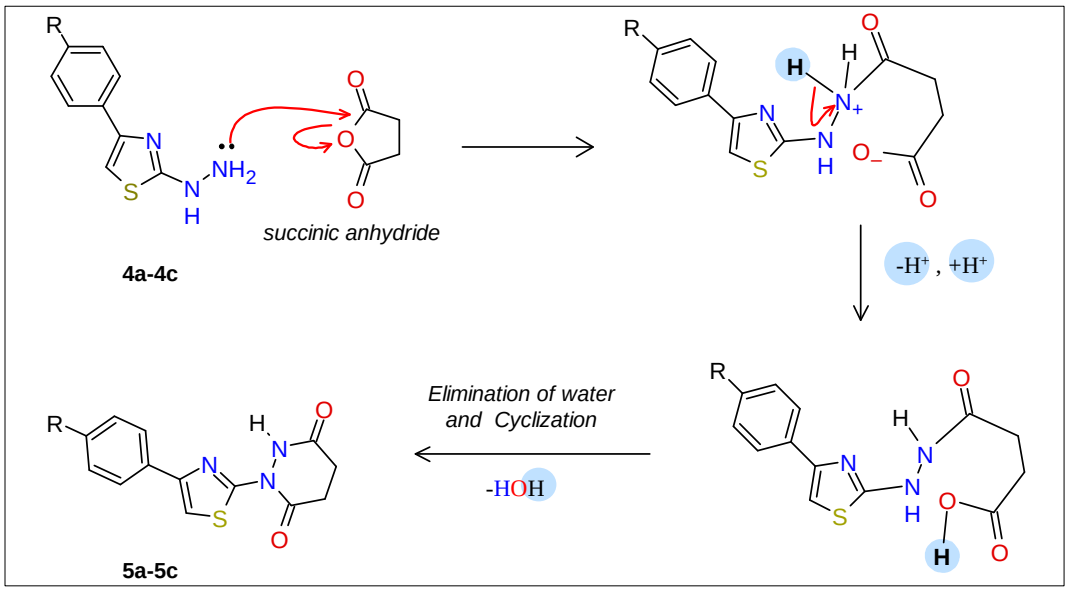
Synthesis of 1-(4-aryl-1,3-thiazol-2-y1) -1,2-diazinane-3, 6-dione (5a-5c)

1-(4-phenylthiazol-2-yl) hexahydropyridazine-3, 6-dione (5a; *General procedure*): A mixture of 4a (1.0 g) and succinic anhydride (0. 52 g) on heating in an oil bath at 190-195 ºC for 45 minutes gave a product. The product was triturated with methanol and filtered to get 1-(4-phenylthiazol-2-yl) hexahydropyridazine-3, 6-dione 5a. Yield (49%, 0.7 g); m.p.203-204 ºC. 1H NMR (DMSO-d_6) δ: 2.85 (s,4H, 2 x CH_2), 7.5 (br. s,4H, Ar-H and H-5), 7.8 (s, 2H, ArH).IR (υ cm^{-1} nujol): 3110 (-NH), 1740 (>C=O); Elemental analysis: Found, C 56.91, H4.23, N 14.933; $C_{13}H_{11}N_3O_2S$, Formula weight: 273.31; requires C 57.14, H 4.02; N 15.38%.

1-[4-(4-methylphenyl)-1, 3-thiazol-2-yl] -1, 2-diazinane -3, 6-dione (5b): Heating 4b (1.0 g) and succinic anhydride (0.48 g) gave 5b. Yield (43%, 0.6 g); m.p. >300ºC.1H NMR (DMSO-d_6) δ: 2.1 (s,3H, CH_3), 2.8 (s,4H, 2 x CH_2), 7.2-7.5 (m,5H, Ar-H and H-5); IR (υ cm^{-1} nujol): 3200 (-NH), 1720 (>C=O) ; Elemental analysis: Found, C 57.87, H 4.21, N 14.01; $C_{14}H_{13}N_3O_2S$, Formula weight:287.34; requires C 58.53; H 4.52, N 14.63%

1-[4-(4-methoxyphenyl)-1, 3-thiazol-2-yl] -1, 2-diazinane -3, 6- dione (5c): Heating 4c (1.0 g) and succinic anhydride (0. 42 g) gave 5c (47%, 0.65 g). mp 127º-129 ºC; 1H NMR (DMSO-d_6) δ: 2.9 (s,4H, 2x CH_2), 3.9 (s,3H, OCH_3), 7.3-7.8 (m,5H, Ar-H and H-5); IR (υ cm^{-1} nujol): 3150 (-NH), 1720 (>C=O); Elemental analysis: Found, C 54.89; H 4.31; N 13.59; $C_{14}H_{13}N_3O_3S$, Formula weight:303.34; requires, C 55.44; H 4.29; N 13.86%.

Result And Discussion



Scheme 2: Proposed mechanism for the formation of 1-(4-aryl-1, 3-thiazol-2-yl)-1, 2-diazinane-3, 6-dione 5a-5c

Condensation of 2-hydrazinyl-4-phenyl-1, 3-thiazole with succinic anhydride resulted in formation of 1-(4-aryl-1, 3-thiazol-2-y1) -1, 2-diazinane-3, 6-dione (5a-5c). The mechanism of cyclization is depicted in Scheme 2. The nucleophilic attack of nitrogen (*hydrazino* NH_2) on electrophilic carbonyl carbon followed by loss of proton and removal of water formed a 6-membered cyclic system namely 1,2-diazinane-3, 6-dione. In the synthesized heterocyclic compounds thiazole ring was attached at position 2 to 1, 2-diazinane-3, 6-dione and these compounds were characterized by elemental analysis and spectral studies. Further, the physicochemical properties of synthesized compounds (5a-5c) were predicted using Chem Axon chemicalize online web server [15, 16] and detailed discussion is as follows:

Physicochemical Properties

For synthesized compounds (5a-5c) the study of physicochemical properties, like logP (octanol/water partition coefficient), logD (distribution coefficient), logS (intrinsic solubility), pKa (acidic and basic), microspecies distribution at different pH and HLB (hydrophilic-lipophilic balance), was carried out using Chem Axon chemicalize online web server [15, 16]. The outcome has been summarized in Table 1 and Table 2.

Table 1: Structural Features of 1-(4-aryl-1,3-thiazol-2-yl)-1,2- diazinane-3,6-diones (**5a-5c)**

Structural Features	Compounds		
	5a (R=H)	**5b (R=CH_3)**	**5c (R=OCH_3)**
Molar mass: g/mol	273.31	287.34	303.34
formula	$C_{13}H_{11}N_3O_2S$	$C_{14}H_{13}N_3O_2S$	$C_{14}H_{13}N_3O_3S$
TPSA $Å^2$	62.3	62.3	71.53
Atom count	30	33	34
Heavy atom count	19	20	21
Rotatable bond count	2	2	3
Ring count	3	3	3
Aromatic ring count	2	2	2
Hetero ring count	2	2	2
FSP3	0.15	0.21	0.21
Hydrogen bond donor count	1	1	1
Hydrogen bond acceptor count	3	3	4

The compound 1-(4-phenyl-1, 3-thiazol-2-yl)-1, 2- diazinane-3, 6-dione 5a, has been found to have strongest acidic pka value as 9.59 and strongest basic pka as 1.1. The compounds 5b and 5c showed acidic and basic pka in the same range. The isoelectric point of compounds shows the trend 5b >5a >5c. The logP and logD pH 7.4 values for compound 5b were found to be higher than 5a and 5c. All compounds (5a-5c) show an increase in logD values at higher pH. This indicates increase in lipophilic character at high pH.

The hydrophilic lipophilic balance (HLB) measures the degree of a molecule being hydrophilic or lipophilic. The higher HLB value of compound 5c compared to 5a and 5b indicates its high lipophilicity. The qualitative solubility category by Chem Axon plugin is predicted as High. All the compounds (5a-5c) show high intrinsic solubility i.e.,

solubility of neutral (non-ionized) species. The solubility predicted at different pH, shows higher solubility of compounds at low pH (1.7) and lower solubility at higher pH (8.0).

Table 2. Physicochemical properties of 1-(4-aryl-1, 3-thiazol-2-yl)-1, 2- diazinane-3, 6-diones (5a-5c)

Properties	Compounds		
	5a (R=H)	5b (R=CH_3)	5c (R=OCH_3)
pKa values			
Strongest acidic pKa:	9.59	9.69	9.28
Strongest basic pKa	1.1	1.1	1.1
Isoelectric point and charge distribution at different pH			
Isoelectric point	5.34	5.39	5.19
pH	Charge		
1.7	0.20	0.20	0.20
4.6	0.00	0.00	0.00
6.5	-0.00	-0.00	-0.00
7.4	-0.01	-0.01	-0.01
8.0	-0.03	-0.02	-0.05
logP, hydrophilic-lipophilic balance (HLB)			
logP	1.686	2.2	1.529
HLB	17.94	17.433	19.121
log D at different pH			
pH	logD		
1.7	1.59	2.10	1.43
4.6	1.69	2.20	1.53
6.5	1.69	2.20	1.53
7.4	1.68	2.20	1.52
8.0	1.68	2.19	1.51
log S (Intrinsic solubility) and solubility at different pH			
logS mg/Ml (Intrinsic solubility)	-2.891 (High)	-3.396 (High)	-2.884 (High)
pH	Solubility [mg/ml]		
1.7	0.44	0.14	0.50
4.6	0.35	0.12	0.40
6.5	0.35	0.12	0.40
7.4	0.35	0.12	0.40
8.0	0.36	0.12	0.42

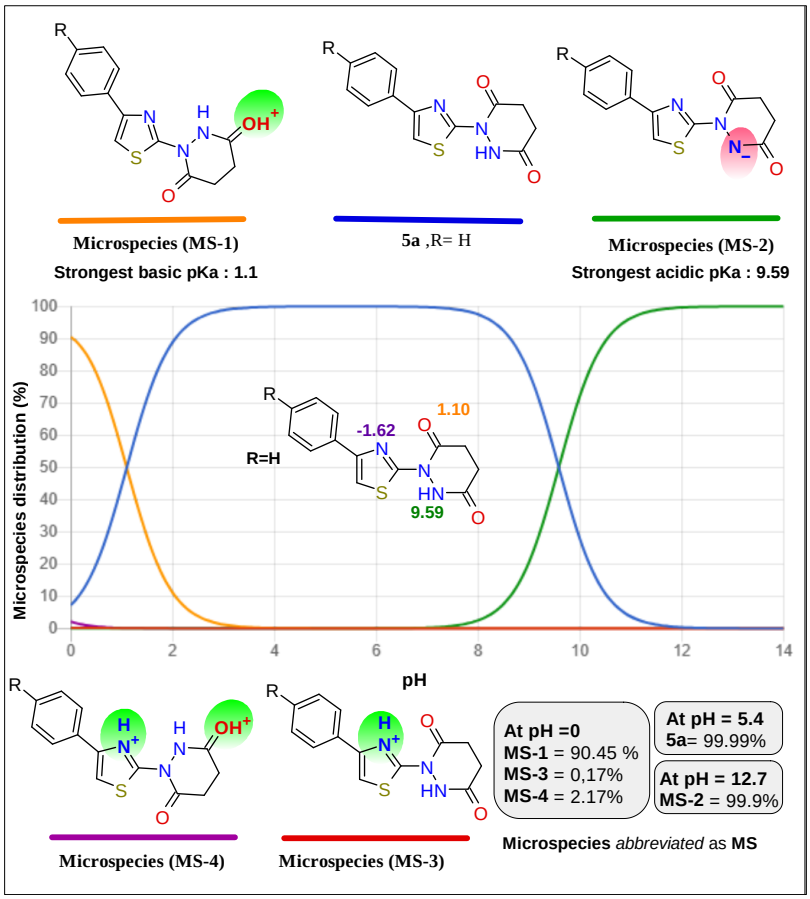


Fig 1: plot of percentage of microspecies v/s pH compound 5a (similar plot observed for 5b and 5c)

Prediction of acidic pKa and Basic pKa

Heterocyclic molecules (5a-5c) have nitrogen and oxygen available, which are the sites that can act as proton donor or acceptor at different pH (Fig1.).

The ionization states of synthesized compounds 5a-5c, were predicted using the ChemAxon web platform, and their pKa values were estimated. For each of the compounds 5a-5c, four additional microspecies are generated at different pH and percentage microspecies distribution at different pH is shown in Fig 1.

At low pH the molecule acts as a base as the carbonyl oxygen of 1, 2-diazinane-3, 6-dione accepts a proton. The formed microspecies MS-1 with protonated oxygen acts as a conjugate acid, with pKa 1.1. At high pH, the molecule acts as an acid, as the nitrogen of 1, 2-diazinane-3, 6-dione loses a proton, the microspecies MS-2 so formed acts as a conjugate base with pKa 9.59. The other two microspecies MS-3 and MS-4 (both conjugate acids) are generated at low pH in negligible percentage. The microspecies MS-3 is formed when nitrogen of thiazole ring accepts a proton. The microspecies MS-4 is formed when both nitrogen of thiazole ring as well as carbonyl oxygen of 1, 2-diazinane-3, 6-dione accept a proton. Chemicalize visualization of microspecies indicate the strongest acidic pKa 9.59 and strongest basic pKa 1.1.

Conclusion

Synthesis of 1-(4-aryl-1, 3-thiazol-2-y1) -1, 2-diazinane-3, 6-diones (5a-5c) was carried out by reaction of 2-hydrazinyl-4-aryl-1, 3-thiazoles with succinic anhydride. The synthesized compounds were characterized by elemental analysis and spectral studies. For study of physicochemical properties Chem Axon chemicalize online web server was used. Chemicalize visualization of microspecies indicate the strongest acidic pKa 9.59 and strongest basic pKa 1.1. All compounds (5a-5c) show high intrinsic solubility. Compounds show higher solubility at lower pH (1.7) and lower solubility at higher pH (8.0). Compounds (5a-5c) show an increase in logD values at higher pH, which indicates increase in lipophilic character at high pH. The high HLB value of compound 5c indicates its high lipophilicity.

[*Note*: The synthetic part of this paper is an unpublished work from the Ph.D. thesis (1993) of the author (Manju Mehta *nee'* Rawat), carried out in Chemistry Department University of Delhi. The research work has been further extended for studies of physicochemical properties by incorporating recently developed cheminformatics tools and updated literature.]

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16. Chemicalize was used for name to structure generation/prediction of *physicochemical* properties/etc, https://chemicalize.com/ developed by ChemAxon (http://www.chemaxon.com)