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Synthesis of 2-(4-aryl-1,3-thiazol-2-yl)-2,3-dihydrophthalazine-1,4-diones and comparative study of physicochemical properties of synthesized compounds and their Tautomeric forms

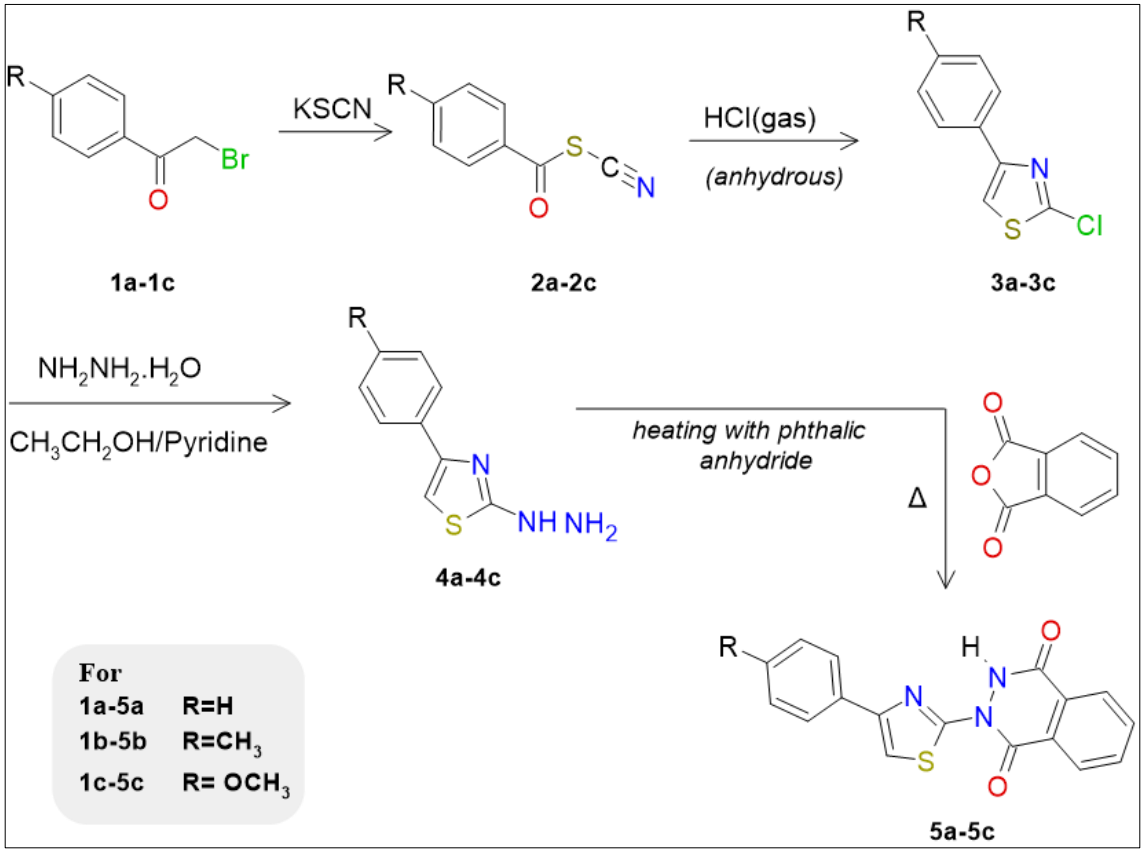
Manju Mehta

Abstract
Phthalazine and Thiazole derivatives have been studied extensively for their broad-spectrum pharmacological, agricultural and biological activities. In the present paper, synthesis of 2-(4-aryl-1,3-thiazol-2-yl)-2,3- dihydrophthalazine-1,4-dione derivatives has been carried out by reaction of 2-hydrazinyl-4-aryl-1,3-thiazole with phthalic anhydride. The synthesized compounds were characterized by spectral analysis. Also, predictive evaluation of 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 for synthesized compounds and their tautomer using Chem Axon chemicalize online software.

Keywords: Thiazolyl-2,3- dihydrophthalazine-1,4-diones, hydrazinylthiazoles, logP, logD, logS, HLB, acidic and basic pKa, microspecies

Introduction
Chemistry of heterocyc1ic compounds has acquired considerable importance and interest because of their pharmacological and biological activities [1]. This wide field of heterocyc1ic compounds includes thiazoles, imidazoles, triazoles, diazines, pyrrazoles, fused heterocyclic moieties etc. Among heterocyc1ic compounds thiazoles hold a valuable position as these are known to be a part of various drugs [2] and biological active compounds [3]. In a similar manner the phthalazine derivatives are known to possess broad spectrum applications [4] as antihypertensive [5, 6], anticonvulsant [7], antidiabetic [8], cardiotonic [9] and anti-tumour agent [10]. These are also used as agrochemicals [11]. Keeping this in view, it was of interest to synthesize heterobicyclic compounds having both thiazole and phthalazine moieties joined together. In the present paper, reaction of 2-hydrazinyl-4-aryl-1,3-thiazole (4a-4c) with phthalic anhydride has been carried out for the synthesis of 2-(4-aryl-1,3-thiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione derivatives (5a-5c)

Scheme 1
Starting from 2-bromo-1-arylethan-1-one (1a-1c), the synthesis of benzoyl thiocyanates (2a-2c), 2-Chloro-4-aryl-1,3-thiazole (3a-3c) and 2-Hydrazinyl-4-aryl-1,3-thiazole(4a-4c) has already been reported [12, 13].



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

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)

Experimental procedure and analytical data reported in literature [12, 13]

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

Experimental procedure and analytical data reported in literature [12, 13]

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

Experimental procedure and analytical data reported in literature [12, 13]

Synthesis of 2-(4-aryl-1,3-thiazol-2-yl)- 2,3-dihydrophthalazine-1,4-diones (5a-5c)

2-(4-phenyl-1,3-thiazol-2-yl)- 2,3-dihydrophthalazine-1,4-dione (5a *General procedure*)

A mixture of 2-hydrazinyl-4-phenyl-1,3-thiazole 4a (1.0 g) and phthalic anhydride (0.8 g) on heating in an oil bath at 180-190º C for 45 minutes gave a product. The product was washed with sodium bicarbonate solution and filtered. It was characterized as 2-(4-phenyl-1,3-thiazol-2-yl)2,3-dihydrophthalazine-1,4-dione 5a. Yield (54%, 0.9 g); m.p.280º C.1H NMR (DMSO-d_6) δ: 7.2-7.8 (m, Ar-H, H-5).IR (υ cm^{-1} nujol): 3200 (-NH), 1700 (>C=O); Elemental analysis: Found C 63.0,H 3.1,N13.22; C $_{17}H_{11}N_3OS$, Formula weight: 321.35; requires C 63.54, H 3.45, N 13.08%.

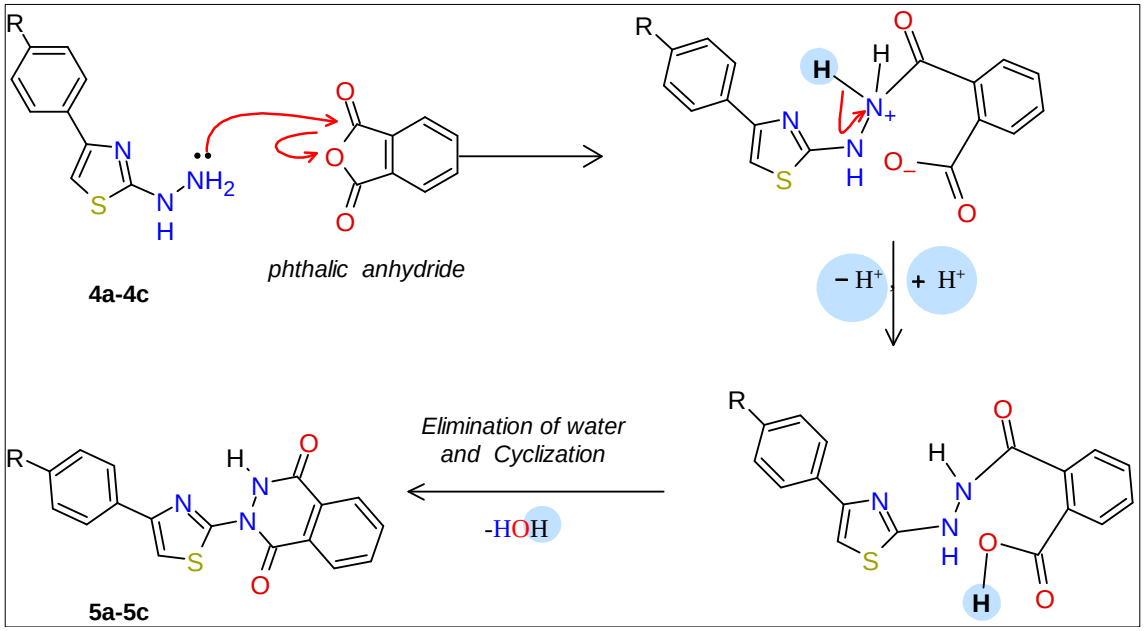
2-[4-(4-methylphenyl)-1,3-thiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (5b)

Heating 2-hydrazinyl-4-(4-methy1phenyl)-1,3- thiazole 4b (1.0 g) and phthalic anhydride (0.72 g) gave 5b Yield (52%, 0.8 g); m.p.163-165 ºC. 1H NMR (DMSO-d_6) δ: 2.1 (s,3H, CH_3), 7.2-7.8 (m, 9H, Ar-H and H-5). IR (υ cm^{-1} nujol): 3200 (-NH), 1710 (>C=O); Elemental analysis: Found C 64.01; H 3.21, N 12.01; $C_{18}H_{13}N_30_2S$, Formula weight: 335.38; requires C 64.46, H 3.91, N 12.53%

2-[4-(4-methoxyphenyl)-1,3-thiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (5c): Heating 2-hydrazinyl-4-(4-methoxyphenyl)-1,3- thiazole 4c (1.9 g) and phthalic anhydride (0.78) gave 5c. Yield (45%, 0.7 g); m.p.143-145 ºC.1H NMR (DMSO-d_6) δ: 3.95 (s,3H, OCH_3), 7.0 (s,1H, H-5), 7.5-8.0 (m, 8H,Ar-H). IR (υ cm^{-1} nujol): 3200 (-NH), 1700 (>C=O); Elemental analysis: Found C 61.21, H 2.93, N 11.12; $C_{18}H_{13}N_3O_3S$, Formula weight: 351.38; requires C 61.53, H 3.73, N 11. 96%.

Result and Discussion

Condensation of 2-hydrazinyl-4-aryl-1,3-thiazoles (4a-4c) with phthalic anhydride resulted in formation of 2-(4-aryl-1,3-thiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione (5a-5c). The mechanism of cyclization is depicted in Scheme 2.



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

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 2,3-dihydrophthalazine-1,4-dione. The synthesized heterobicyclic compounds had thiazole ring attached at position 2 to 2,3-dihydrophthalazine-1,4-dione and these compounds were characterized by elemental analysis and spectral studies. Further, the synthesized compounds (5a-5c) exist in corresponding tautomeric forms (6a-6c) Figure 1.

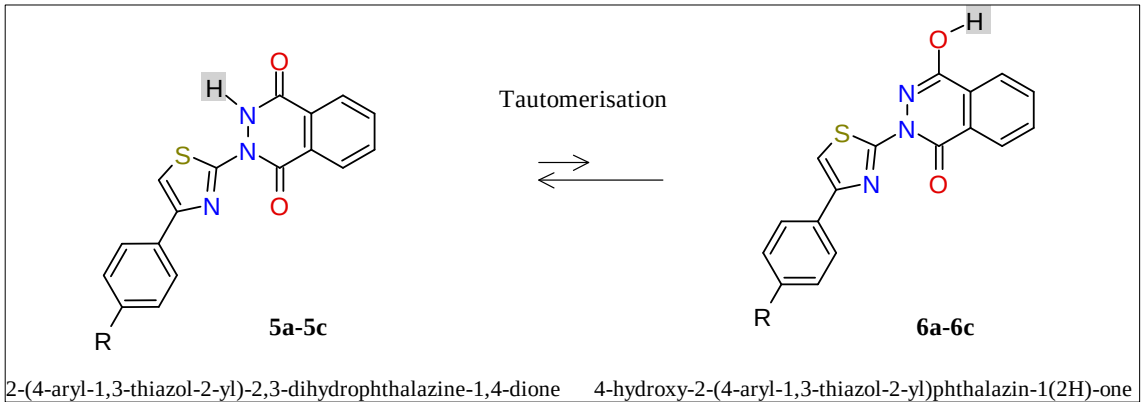


Fig 1: Tautomerisation in compounds 5a-5c and formation of corresponding tautomers 6a-6c

The physicochemical properties of synthesized compounds (5a-5c) and corresponding tautomeric forms (6a-6c) were predicted using Chem Axon chemicalize online web server [14, 15] and detailed discussion is as follows:

Physicochemical properties

For physicochemical properties of synthesized compounds, like logP (octanol/water partition coefficient), TPSA (topological polar surface area), logD (distribution coefficient), HLB (hydrophilic-lipophilic balance), logS (intrinsic solubility), pKa (*acidic* and *basic*), and microspecies distribution at different pH, online web server Chem Axon chemicalize was used and the data has been compiled in Table 1.

The 2-(4-phenyl-1,3-thiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione derivative 5a, has been found to have acidic pKa value 3.47 and basic pKa as -0.8. The compounds 5b and 5c showed acidic and basic pKa in the same range. The corresponding Tautomers 6a, 6b and 6c showed higher acidic pKa of 6.41, 6.42 and 6.3 respectively. None of the Tautomers showed basic pKa. The isoelectric point of the compounds was observed to follow the trend 5b>5a>5c. Isoelectric point was not observed for any of the tautomers.

The logP value for compound 5a was 3.373 and for its tautomer 6a, a higher value (logP 4.193) was observed. The same pattern was observed for compounds 5b, 5c and their corresponding tautomers 6b and 6c. The higher logP values of tautomers (6a-6c) compared to corresponding compounds (5a-5c) is attributed to their high lipophilicity. The hydrophilic lipophilic balance (HLB) measures the degree of a molecule being hydrophilic or lipophilic. The HLB values of compounds followed the order 5a>5c>5b. The same trend of HLB values was observed for corresponding tautomers 6a>6c>6b. The HLB values of compounds (5a-5c) were higher compared to their corresponding tautomers (6a-6c). These observations indicate high lipophilicity of tautomers. For compounds (5a-5c) a decrease in logD values at higher pH was observed. Similar pattern of decrease in logD values with increasing pH was observed for tautomers (6a-6c). This indicates a decrease in lipophilic character of compounds (5a-5c) and corresponding tautomers (6a-6c) at higher pH.

The logS values for all compounds (5a-5c) and their tautomers (6a-6c) were low (< 0.01mg/mL) and indicate their poor solubility. The solubility predicted at different pH shows relative increase in solubility of compounds (5a-5c) at higher pH. This is due to increase in hydrophilic character of compounds (5a-5c) at higher pH. However, the tautomers (6a-6c) were found to be insoluble at any pH and this may be attributed to their high lipophilicity compared to parent compounds (5a-5c). The topological polar surface area (TPSA) value for compound 5c is higher than the corresponding compounds 5a and 5b. The tautomers (6a-6c) have high TPSA value compared to corresponding compounds (5a-5c).

Table 1: Physicochemical properties of 2-(4-aryl-1,3-thiazol-2-yl)-2,3-dihydrophthalazine-1,4-diones (5a-5c) and corresponding tautomers (6a-6c) by Chem Axon chemicalize

Properties	**Compounds 5a-5c and their tautomers 6a-6c**					
	R=H		**R=CH_3**		**R=OCH_3**	
	5a	**6a (*Tautomer*)**	**5b**	**6b (*Tautomer*)**	**5c**	**6c (*Tautomer*)**
Molar mass: g/mol	321.35	321.35	335.38	335.38	351.38	351.38
formula	$C_{17}H_{11}N_3O_2S$	$C_{17}H_{11}N_3O_2S$	$C_{18}H_{13}N_3O_2S$	$C_{18}H_{13}N_3O_2S$	$C_{18}H_{13}N_3O_3S$	$C_{18}H_{13}N_3O_3S$
TPSA $Å^2$	62.3	65.79	62.3	65.79	71.53	75.02
Strongest acidic pKa:	3.47	6.41	3.57	6.42	3.24	6.3
Strongest basic pKa	-0.8	Not Observed	-0.8	Not Observed	-0.8	Not Observed
Isoelectric point	1.34	Not Observed	1.38	Not Observed	1.22	Not Observed
LogP	3.373	4.193	3.887	4.706	3.215	4.035
HLB	12.443	12.155	7.616	7.328	9.208	8.92
Values of Distribution coefficient, logD and Solubility at different pH for Compounds 5a -5c and their Tautomers 6a-6c						
logD / **pH**	**5a**	**6a (*Tautomer*)**	**5b**	**6b (*Tautomer*)**	**5c**	**6c (*Tautomer*)**
1.7	3.37	4.19	3.88	4.71	3.20	4.04
4.6	2.62	4.19	3.16	4.70	2.40	4.03
6.5	2.43	3.84	2.95	4.36	2.27	3.62
7.4	2.43	3.16	2.94	3.69	2.27	2.90
8.0	2.43	2.60	2.94	3.12	2.27	2.33
Solubility						
Intrinsic solubility: mg/ml	-6.251 Low	-6.057 Low	-6.745 Low	-6.551 Low	-6.221 Low	-6.027 Low
Solubility [mg/ml] at different pH						
Solubility / **pH**	**5a**	**6a (*Tautomer*)**	**5b**	**6b (*Tautomer*)**	**5c**	**6c (*Tautomer*)**
1.7	0.00	0.00	0.00	0.00	0.00	0.00
4.6	0.00	0.00	0.00	0.00	0.01	0.00
6.5	0.19	0.00	0.05	0.00	0.38	0.00
7.4	1.53	0.00	0.41	0.00	3.03	0.00
8.0	6.10	0.01	1.64	0.00	12.07	0.02

Prediction of *acidic* pKa *and Basic* pKa

Heterocyclic molecules 2-(4-aryl-1,3-thiazol-2-yl) 2,3-dihydrophthalazine-1,4-dione derivatives (5a-5c) have nitrogen and oxygen available, which are the sites that can act as proton donor or acceptor at different pH. 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, two additional microspecies are generated at different pH and the percentage microspecies distribution at different pH is shown in Figure 2. Similarly, for each of the tautomer 6a-6c an additional microspecies is generated at different pH and the percentage microspecies distribution at different pH is shown in Figure 3.

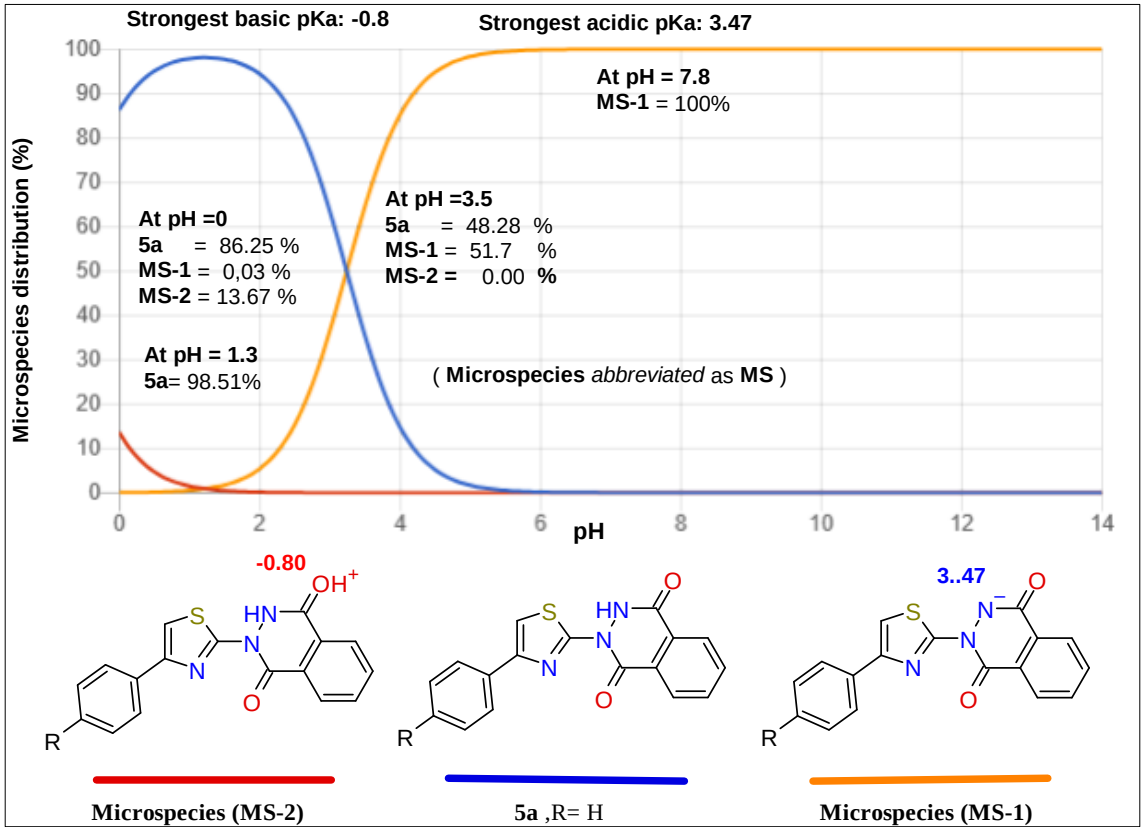


Fig 2: Plot of percentage of microspecies v/s pH for compound 5a, R=H (similar plot observed for 5b, R=CH_3 and 5c, R= OCH_3)

At low pH (pH=0) the molecule 5a acts as a base as the carbonyl oxygen of 2,3-dihydrophthalazine-1,4-dione accepts a proton. The formed microspecies MS-2, with protonated oxygen acts as a conjugate acid, with pKa -0.8. The microspecies MS-2 is formed 13.6% at pH 0. It exists up to pH 1.3. Microspecies MS-2 does not exist above pH 1.3.

At high pH (pH=7.8), the molecule 5a acts as an acid, as the nitrogen of 2,3-dihydrophthalazine-1,4-dione loses a proton. The microspecies MS-1 so formed acts as a conjugate base with pKa 3.47. The microspecies MS-1 exist 100% at pH 7.8. Microspecies MS-1 exist in negligible amount at lower pH. The compound 5a is major species (98.5%) at pH 1.3. The compound 5a and its conjugate base MS-1 are present in nearly equal amount at pH 3.5.

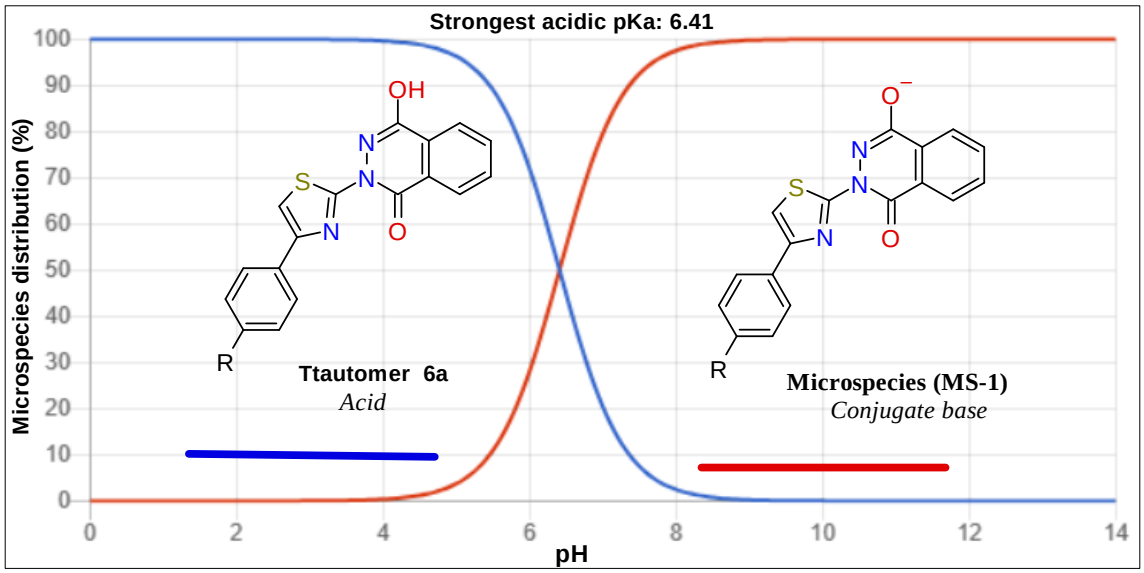


Fig 3: Plot of percentage of microspecies v/s pH for tautomer 6a, R=H (similar plot observed for 6b, R=CH_3 and 6c, R= OCH_3)

Similarly, for each of the tautomer 6a-6c an additional microspecies is generated at different pH and the percentage microspecies distribution at different pH is shown in Figure 3. The tautomer 4-hydroxy-2-(4-phenyl-1,3-thiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione 6a, acts as an acid as the hydroxy group loses a proton. The microspecies MS-1, so formed acts as a conjugate base. The tautomer (acid) shows strongest acidic pKa 6.41. The tautomer 6a exist as major species (100%) at low pH 1.2-2.0. The microspecies MS-1 exist as a major species (100%) at pH 10.8. The tautomer 6a and its conjugate base MS-1 are present in nearly equal

amount at pH 6.4. The basic pKa is not observed for tautomers 6a-6c.

Conclusion

Synthesis of 2-(4-aryl-1,3-thiazol-2-yl) 2,3-dihydrophthalazine-1,4-dione has been carried out by reaction of 2-hydrazinothiazole with phthalic anhydride. The synthesized compounds were characterized by spectral analysis. The study of physicochemical properties of compounds and their tautomers was carried out using online web server Chem Axon chemicalize. The logP and HLB values of tautomers indicate their high lipophilicity compared to corresponding compounds 5a-5c. The logS values for all compounds are low and indicate their poor solubility. The compounds 5a-5c showed acidic and basic pKa in the same range, however their tautomers 6a-6c showed only acidic pKa. The topological polar surface area (TPSA) value for methoxy- substituted compound 5c is higher than the corresponding compounds 5a and 5b. The tautomers 6a-6c have high TPSA value compared to corresponding compounds 5a-5c.

[*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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14. Calculator Plugins were used for structure property prediction and calculation of logP, pKa, logD, Solubility Predictor; ChemAxon (http://www.chemaxon.com)
15. Chemicalize was used for name to structure generation/prediction of physicochemical properties/etc, https://chemicalize.com/ developed by ChemAxon (http://www.chemaxon.com)