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Article

Synthesis of Novel Spiro [imidazolidine- pyrazoline]-2, 4-dione Derivatives

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ABSTRACT

The pharmaceutical importance of spiro-imidazolidinedione derivatives is well established. Here, we communicate the synthesis of new spiro [imidazolidine-pyrazoline]- 2,4-diones in two steps. The first step involves the preparation of 5-ary1idene imidazolidine-2,4-dione derivatives by well-known Knoevenagel reaction involving condensation of aromatic aldehydes and imidazolidine-2,4-dione. In the second step, reaction of diazomethane with 5-ary1idene imidazolidine-2, 4-dione resulted in formation of new spiro [imidazolidine-pyrazoline] 2,4-dione derivatives. The synthesized spiro compounds were characterized by spectral analysis. Computational studies have been utilized to explain the stability of tautomeric forms of synthesized compounds. The Swiss ADME studies indicate suitable physiochemical properties, drug-likeliness features, and good oral bioavailability.

Key words: Spiro [imidazolidine-pyrazoline]-2, 4-diones, diazomethane, 5-arylidene imidazolidine-2, 4- diones

1. INTRODUCTION

Imidazolidine-2, 4-dione derivatives, commonly known as hydantoin derivatives exhibit diverse biological and pharmacological activities [1,2]. Phenytoin (**1**) [3-5,6a] is an anticonvulsant that is used to control certain type of seizures, by decreasing abnormal electrical activity in the brain. Nitrofurantoin (**2**) [6b,7-9] is an antibiotic and is used to treat urinary tract infections and bladder infections. Mephenytoin (**3**) [6c] is a drug used to control seizures and works by slowing down impulses in the brain. Nilutamide (**4**) [6d,10,11] sold under the brand names Nilandron and Anandron, is a nonsteroidal antiandrogen (NSAA) which is used in the treatment of prostate cancer. Spirohydantoin derivatives constitute one of the important classes of heterocyclic compounds with immense pharmaceutical importance [12-14] and biological activities. For example, autotaxin inhibitor (**5**) [15], Tetratoin (**6**) [16] an anticonvulsant, Sorbinil (**7**) [17] an aldose reductase inhibitor, and Spiromustine (**8**) [18] an antitumor **(Figure 1)**.

In the present study, Knoevenagel reaction involving condensation of hydantoin (**9**) and aromatic aldehydes (**10a-d**) has been used for synthesis of 5-ary1idene hydantoin derivatives (**11a-d**) [19-21]. The reaction of diazomethane with 5-ary1idene hydantoin derivatives (**11a-d**) resulted in the formation of new spirohydantoin derivatives namely spiro [imidazolidine-pyrazoline]-2,4-dione derivatives (12a-d). The synthetic strategy has been summarized in **Scheme 1.**

2. 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.

2.1. Synthesis of 5-Ary1idene Hydantoin Derivatives (11a-d)

2.1.1. General procedure

2.1.1.1. (5E)-5-benzylideneimidazolidine-2, 4-dione (11a)

To a mixture of hydantoin (**9**) (10 mmol, 1.0 g) in methanol (20 mL) containing sodium methoxide (0.5 g), a solution of benzaldehyde (**10a**) (10 mmol, 1.0 mL) in methanol (5 mL), was added drop-wise, with stirring at room temperature. After complete addition, the mixture further stirred for 4 h at room temperature. Solvent was distilled off and to residue ice was added. The mixture was neutralized with dil. HCl. The product obtained was filtered and washed thoroughly with water to obtain 5-benzylideneimidazolidine-2, 4-dione (**11a**) as white solid. The crude product was recrystallized from methanol; Yield: (6.5 mmol, 1.2 g, 63.8%); m. p. 220-222°C [22].

Similarly, **11b-d** were obtained as white solid from corresponding arylaldehydes (**10b-d**).

All melting points recorded were in agreement with the literature values [19-23].

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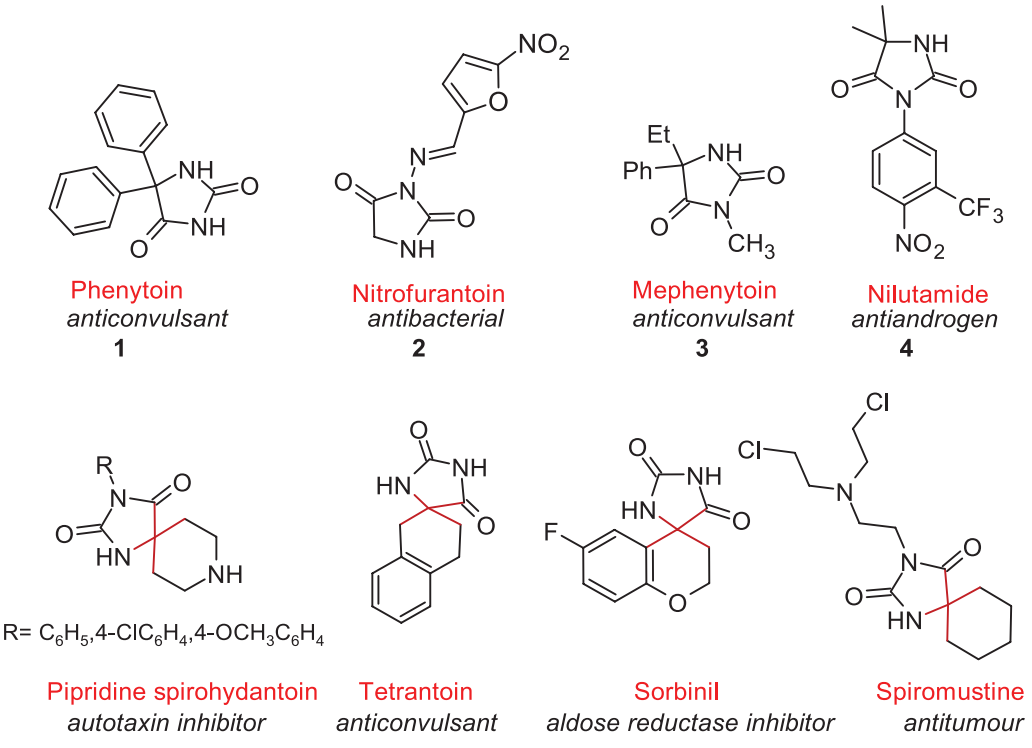


Figure 1: Some examples of hydantions and spirohydantoins of medicinal importance.

2.1.1.2. (5*E*)-5-[(4-methylphenyl)methylidene]imidazolidine-2,4-dione(11b)

It was synthesized by the reaction of hydantoin and 4-methyl benzaldehyde (**10b**); Yield: (7.4 mmol,1.5 g, 74.2%); m. p. 275-276°C.

2.1.1.3. (5*E*)-5-[(4-methoxyphenyl)methylidene]imidazolidine-2,4-dione (11c)

It was synthesized by the reaction of hydantoin and 4-methoxybenzaldehyde (**10c**); Yield: (2.3 mmol, 0.5.g, 22.9%); m. p. 211-212°C.

2.1.1.4. (5*E*)-5-[(4-chlorophenyl)methylidene]imidazolidine-2,4-dione (11d)

It was synthesized by the reaction of hydantoin and 4-chlorobenzaldehyde (**10d**). Yield: (7.6 mmol, 1.7g, 76.5%); m. p.292-294°C.

2.2. Preparation of Diazomethane [24]

Diazomethane was prepared from toluene-4-sulfonyl chloride followed by series of reactions using standard procedures.

2.3. Synthesis of Spiro [Imidazolidine-Pyrazoline]-2,4-Dione Derivatives (12a-d)

2.3.1. General procedure

2.3.1.1. Preparation of 6-phenyl-1, 3, 7, 8-tetraazaspiro [4.4]non-7-ene-2,4-dione (12a)

5-Benzylideneimidazolidine-2, 4-dione (**11a**) (2.6 mmol 0.5 g) was taken in dry ether solution. To this diazomethane was passed in excess, for about 30–45 min. The solution color changed to dark yellow. The reaction mixture was then kept in the refrigerator at 0° for 48 h. The ether was distilled off at room temperature, under reduced pressure. The product **12a** was obtained as 1ight yellow solid. Yield (0.9 mmol, 0.2 g, 33.3%); m. p. 180–182°C (Dec.) 1H NMR (DMSO-d_6) δ: 2.60 (s, 2H, CH_2N), 3.3 (s, 1H, NH, D_2O exchangeable), 4.8(s, 1H, CH), 7.25 (s, 5H, ArH), 7.6-7.7 (*br*-s, NH, D_2O exchangeable).

IR (υ cm^{-1} nujol): 3310 and 3500 (-NH), 1700 and 1750 (C=O)

Elemental analysis: Found C 57.01, H 4.50, N 25.01 $C_{11}H_{10}N_4O_2$; requires C57.38, H 4.37, N 24.33%

Similarly, **12b-d**, were prepared from 5-ary1idene hydantoin derivatives (**11b-d**)

2.3.1.2. 6-(4-methylphenyl)-1, 3, 7, 8-tetraazaspiro [4.4]non-7-ene-2,4-dione(12b)

Diazomethane was passed through a solution of 5-(4- methylbenzylidene) imidazolidine-2, 4-dione (**11b**) (2.5 mmol, 0.5 g) in ether. The reaction mixture on working up gave **12b**. Yield: (0.8 mmol, 0.2g, 33.3%) m. p. 195°C (Dec).

1H NMR (DMSO-d6) δ: 2.1 (s, 3H, CH_3), 2.62(s, 2H, CH_2-N) 3.2(s, 1H, NH, D_2O exchangeable), 4.75 (s, 1H, CH); 7.0-7.25 (m, 4H, Ar-H), 7.7 (br-s NH, D_2O exchangeable)

IR (υ cm^{-1} nujol): 3310 and 3500 (NH), 1700 and 1745 (C=O)

Elemental analysis: Found C 58.91, H 4.80, N 22.51; $C_{12}H_{12}N_4O_2$ requires C 59.01, H 4.94, and N 22.93%.

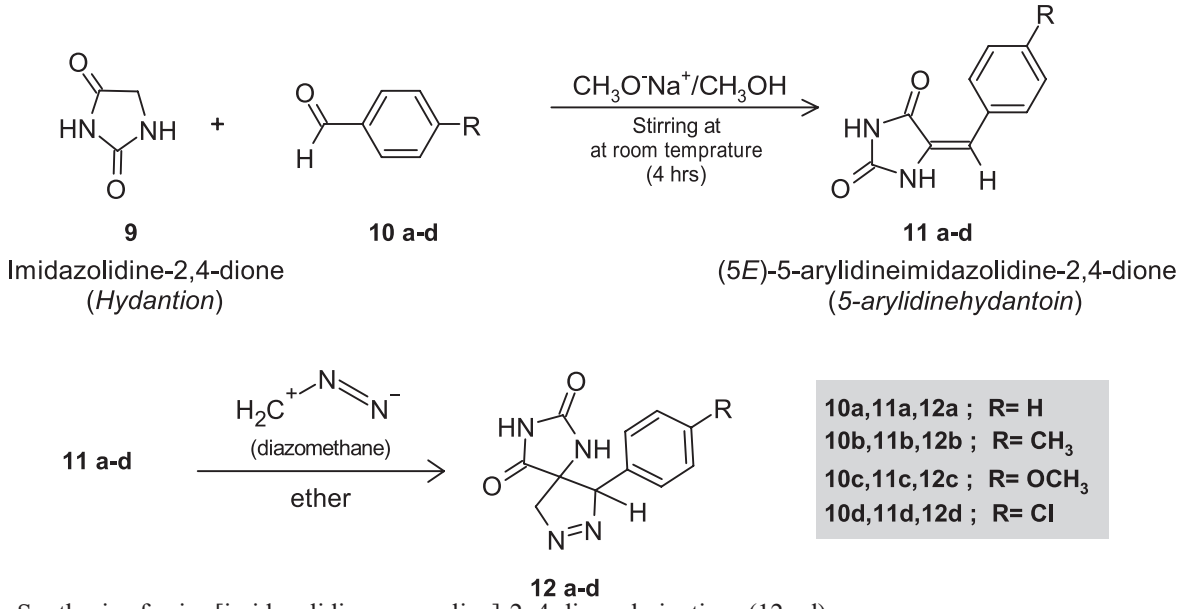
2.3.1.3. 6-(4-methoxyphenyl)-1, 3, 7, 8-tetraazaspiro [4.4] non-7-ene-2,4-dione (12c)

Diazomethane was passed through a solution of 5-(4-methoxybenzylidene)-imidazolidine-2, 4-dione (**11c**) (2.3 mmol 0.5 g) in ether. The reaction mixture on working up gave **12c** (Yield: 0.8 mmol, 0.2 g, 33.8%) m. p. I70-172°C.

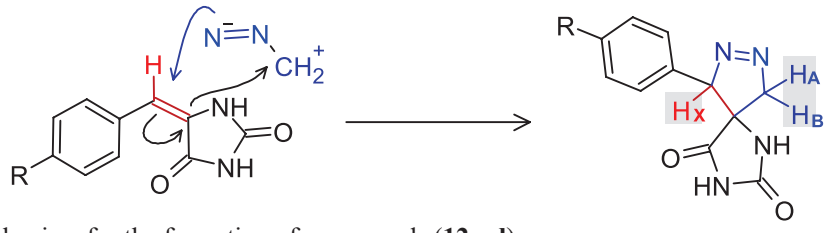
1H NMR (DMSO-d_6) δ: 2.70 (s, 2H, CH_2N), 3.3 (s, 1H, NH D_2O exchangeable), 3.95 (s, 3H, OCH_3), 4.9 (s, 1H, CH), 7.1 and 7.4 each d, J=9Hz, 2x2H, ArH).

IR (υ cm^{-1} nujol): 3200-3310 and 3500 (NH), 1710 and 1750 (C=O).

Elemental analysis Found C 55.01, H 4.59, N 21.32; $C_{12}H_{12}N_4O_3$ requires C55.38, H 4.64, N 21.52%.



Scheme 1: Synthesis of spiro [imidazolidine-pyrazoline]-2, 4-dione derivatives (12a-d).



Scheme 2: Suggested mechanism for the formation of compounds (**12a-d**).

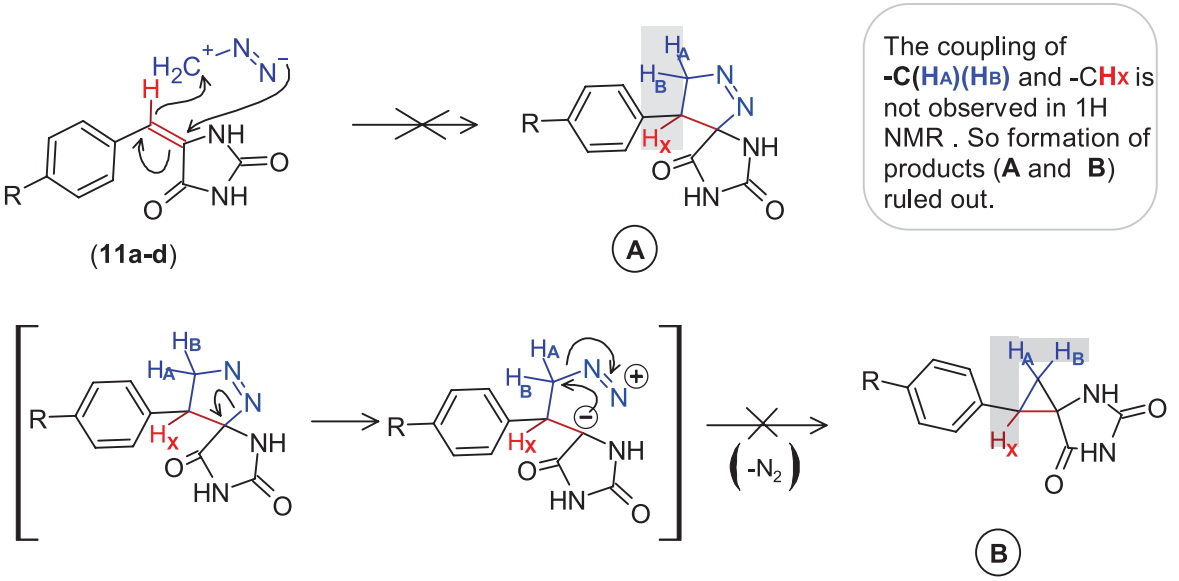


Figure 2: Ruling out possibility of formation of products **A** and **B**.

2.3.1.4. 6-(4-chlorophenyl)-1, 3, 7, 8-tetraazaspiro [4.4]non-7-ene-2,4-dione (12d)

Diazomethane was passed through a solution of 5-(4-chlorobenzy1idene)-imidazolidine-2, 4-dione (**11d**) (2.3 mmol 0.5 g) in ether. The reaction mixture on working up gave **12d** as white crystalline solid (yield: 1.3 mmol, 0.35 g, 59.3%). m. p. 168°C.

1HNMR (DMSO-d_6) δ: 2.7 (s, 2H, CH_2-N), 3.3 (s, 1H, NH, D_2O exchangeable), 4.85 (s, 1H, CH), 7. 32 (s, 4H, ArH), 7.75 (br-s, NH, D_2O exchangeable)

IR (υ cm^{-1} nujol): 3300 and 3500 (NH), 1700 and 1750 (C=O),

Elemental analysis: Found C 49.37, H 3.52, N 21.01; C_{11} $H_9C1N_4O_2$ requires C 49.91, H 3.42, N 21.16%.

3. RESULTS AND DISCUSSION

Passing diazomethane to a solution of (5E)-5-benzylideneimidazolidine-2,4-dione (**11a**) in ether followed by cooling and distilling off ether under reduced pressure gave 6-phenyl-1,3,7,8-tetraazaspiro [4.4]

non-7-ene-2,4-dione (**12a**) (**Scheme 2**). Structure of the product was established by the spectral data. In the present case, diazomethane behaves as electrophile and adds on olefinic bond (11a) to form pyazoline [25] (**Scheme 2**).

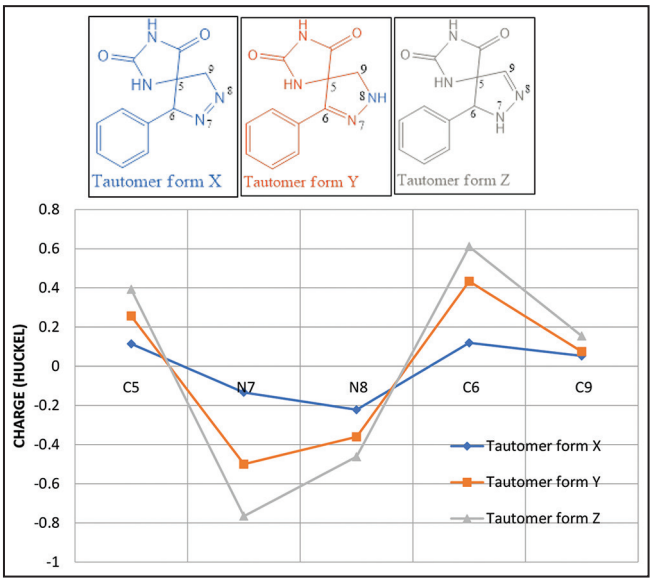


Figure 3: Charge density profile of possible tautomers X, Y, and Z of spirohydantoin 12a.

Table 1: Selected data of charge density and bond length profile in spirohydantoin 12a.

Charges (Huckel)	**C5**	**C6**	**N7**	**N8**	**C9**
Tautomer X	0.11399	0.119267	−0.13402	−0.22256	0.052467
Tautomer Y	0.142359	0.314105	−0.3663	−0.13839	0.021812
Tautomer Z	0.136394	0.177327	−0.26544	−0.10076	0.079888
Bond Length (Å)	C5 –– C6	C6–– N7	N7–– N8	N8––C9	C9–– C5
Tautomer X	1.523	1.47	1.248	1.47	1.523
Tautomer Y	1.497	1.26	1.8517	1.453	1.523
Tautomer Z	1.497	1.26	1.8517	1.453	1.523

However, there may be possibility of formation of compound A or B (**Figure 2**). Had the structure of the product been A or B, the coupling would have been observed for protons $\mathbf{H_X}$, $\mathbf{H_A}$ and $\mathbf{H_B}$. Since no such coupling was observed in 1H NMR of the obtained product, the possibility of the formation of product A or product B has been ruled out. The structure of the product was unambiguously assigned as 6-phenyl-1, 3, 7, 8-tetraazaspiro [4.4]non-7-ene-2,4-dione (**12a**). Similarly, the structures of the other products, **12b-d** were established by spectral data.

3.1. Computational Studies

3.1.1. Tautomer forms of spirohydantoins (12a-d) and comment on their stability

All the spirohydantoins (**12a-d**) have three tautomer forms. Chemical computations were performed to investigate stabilities for tautomer forms (**X**, **Y** and **Z**) of spirohydantoin **12a** by calculating charge density (Huckel) using the Chem Draw Ultra 12.0 software package. For tautomer Y and Z, the C-C bond length (**C5-–- C6**) and C-N bond length (**C6-–N7**) are calculated to be 1.497 Å and 1.26 Å, respectively. The **C5-–C6** bond length for tautomer **Y** and **Z** is found to be 0.026 Å shorter than C**5-– C6** bond length of tautomer **X**. Similarly, the **C6-–N7** bond length for tautomer **Y** and **Z** is found to be 0.021 Å shorter than C**6-–N7** bond length of tautomer **X**.

The charge densities in tautomer **Y** and **Z** are calculated to be 0.142359 and 0.136394, respectively, at **C5** spiral carbon. At **C6**, the values are calculated to be 0.314105 and 0.177327, respectively. These values are greater than the charge densities on the same atoms in tautomer **X** (**Table 1**). This clearly indicates that **C5** and **C6** atoms in tautomer **X** have strong intrinsic properties than the other two tautomers **Y** and **Z**. Hence, tautomer **X** is more stable than the other two tautomers **Y** and **Z** [26]. The charge distribution on all these atoms has been shown graphically (**Figure 3**).

The stability of tautomer **X** is further supported by the lowest energy value of −80.8407 kJ/mol as calculated using Avogadro software. The energy values for tautomer **X**, **Y,** and **Z** as predicted are **−80.8407 kJ/mol**, 34.1404 kJ/mol, and 37.5408 kJ/mol, respectively.

3.2. Physicochemical Data of Spirohydantoins (12a-d) [27]

The ADME properties of synthesized compounds are predicted using Swiss ADME and LD_{50} predicted by ProTox-II, an online web server. The computational physicochemical data of compounds (**12a-d)** exhibit their high-water solubility and moderate lipophilicity. These compounds follow Lipinski's rule without any violation indicating their potential to convert into a drug, provided they show potential biological activity. Compounds **12a-d,** do not cross the blood-brain

Table 2: ADMET data for spiro [imidazolidine-pyrazoline]-2,4-dione derivatives (12a-d).

Compounds Mol. Mass ADMET properties	**12a $C_{11}H_{10}N_4O_2$ 230.22gmol^{-1}**	**12b $C_{12}H_{12}N_4O_2$ 244.25gmol^{-1}**	**12c $C_{12}H_{12}N_4O_3$ 262.27gmol^{-1}**	**12d $C_{11}H_9ClN_4O_2$ 264.67gmol^{-1}**
Consensus LogP	0.51	0.82	0.48	1.05
LogS (*Water solubility*)	−1.65 (*Very soluble*)	−1.96 (*Very soluble*)	−1.73 (*Very soluble*)	−2.25 (*Soluble*)
TPSA (A^0)	82.92	82.92	92.15	82.92
BBB permeation	No	No	No	No
GI absorption	High	High	High	High
Skin permeation (cm/s)	−7.49	−7.31	−7.69	−7.25
Lipinski rule	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation
Bioavailability score	0.55	0.55	0.55	0.55
LD_{50}(mg/kg)	500	500	6200	320
Toxicity class	*Class*-4	*Class*-4	*Class*-6	*Class*-4

barrier (**Table 2**) and have good bioavailability. The toxicity study shows compound **12c** to be non-toxic with LD_{50} 6200 mg/kg.

4. CONCLUSION

Synthesis of new spiro[imidazolidine-pyrazoline]- 2,4-diones was carried out in two steps where Knoevenagel reaction of aromatic aldehydes and imidazolidine-2,4-dione was carried out followed by their reaction with diazomethane. The synthesized compounds were characterized by spectral analysis as spiro[imidazolidine-pyrazoline]-2,4-diones. Computational studies were carried out to explain the stability of tautomeric forms of synthesized compounds. Swiss ADME studies indicated suitable physiochemical properties, drug-likeliness features and good oral bioavailability. Using ProTox-II online web server, toxicity study was carried out for synthesized compounds. All computational data has been summarised in Tables 1 and 2.

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****Bibliographical Sketch***

Dr. Bhupinder Mehta received the B.Sc. Hons, M.Sc. and Ph.D. degrees in Chemistry from University of Delhi, India, in 1981, 1983, and 1987 respectively. He joined the teaching profession in 1988 and is presently working as an Associate Professor in the Department of Chemistry, Swami Shraddhanand College, University of Delhi. His teaching area involves organic chemistry and agricultural chemistry. He has published nine research papers. Co-authored a book entitled 'ORGANIC CHEMISTRY' Bhupinder Mehta and Manju Mehta; Published by PHI Learning Pvt. Ltd. New Delhi; Year of publication for Second Edition (Pages: 1204): July -2015; Print ISBN: 9788120351264 and eBookISBN: 9789390464388. ORCID ID: 0000-0003-4101-054X