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Original article

Synthesis, bioassay, and QSAR study of bronchodilatory active 4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles

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ABSTRACT

A statistically significant QSAR model describing the bioactivity of bronchodilatory active 4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles ($N = 41$, $n = 8$, $R^2 = 0.824$, $R^2_{cv} = 0.724$, $F = 18.749$, $s^2 = 0.0018$) was obtained employing CODESSA-Pro software. The bronchodilatory active 4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles **17**–**57** were synthesized through a facile approach *via* reaction of 1-alkyl-4-piperidones **1**–**4** with ylidenemalononitriles **5**–**16** in methanol in the presence of sodium. The bronchodilation properties of **17**–**57** were investigated *in vitro* using isolated guinea pig tracheal rings pre-contracted with histamine (standard method) and compared with theophylline (standard reference). Most of the compounds synthesized exhibit promising bronchodilation properties especially, compounds **25** and **28**.

1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are both prevalent respiratory diseases that affect millions of people all over the world [1]. Asthma affects about 300 million people worldwide, and is characterized by an increase in inflammatory cell population in the epithelium and submucosa of the airways [2]. There are two main effects of asthma pathophysiology: (i) airway inflammation and (ii) smooth muscle dysfunction which has led to two categories of medicine used in asthma treatment: anti-inflammatory drugs and bronchodilators. To treat the inflammatory component of asthma, inhaled corticosteroids are used, whereas inhaled β_2-agonists are the most effective bronchodilators, offering proven benefits in reducing this disease [3,4]. COPD is the fourth leading cause of death and is projected to rise to third place by 2020 [5]. COPD is most commonly associated with cigarette smoking but other risk factors include air pollutants and occupational dust. This debilitating disease is characterized by a progressive airflow limitation that is only partially reversible. Treatment guidelines emphasize the use of bronchodilators at all stages of the disease with a combination of long-acting bronchodilators recommended for patients with moderate to severe COPD [6].

The present work reports the synthesis and bronchodilation properties of novel 4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles. Our interest in these compounds stems from our previous program directed towards investigation of bio-active agents [7] especially those characterized by vasodilation properties [8,9]. Our recent publication on the vasorelaxant properties of 4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles in isolated thoracic aortic rings of rats pre-contracted with norepinephrine hydrochloride [9], stimulated an investigation of the muscle relaxant properties of the analogs described in this paper, as bronchodilations. Whereas, the receptors assumed to be involved in both pharmacological mode of actions are somewhat correlated (α/β-adrenoceptors), the selectively of the

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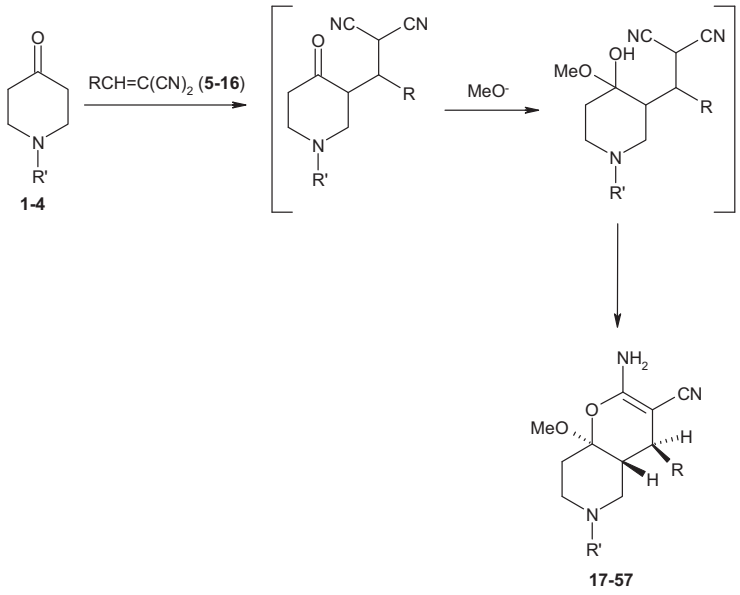
effective agents is questionable. Publications reporting the smooth muscle relaxation and vasodilation properties of pyrano[3,2-*c*] pyridines also motivated the present work [10–12]. Quantitative structure–activity relationship (QSAR) studies are also considered in the present work for validating the observed pharmacological properties of the investigated bronchodilatory compounds and also for determining the most important structure parameters controlling activity.

2. Results and discussion

2.1. Chemistry

The targeted analogs were prepared following our recently published procedure [9] *via* the reaction of 1-alkyl-4-piperidones **1**–**4** with ylidenemalononitriles **5**–**16** in methanol in the presence of sufficient sodium to afford the 6-alkyl-2-amino-4-aryl-



1, R' = Me
2, R' = Et
3, R' = 1-Propyl
4, R' = Benzyl

5, R = Ph
6, R = 2-naphthyl
7, R = 4-BrC_6H_4
8, R = 4-ClC_6H_4
9, R = 2,4-$Cl_2C_6H_3$
10, R = 4-FC_6H_4
11, R = 4-$H_3CC_6H_4$
12, R = 4-$H_3COC_6H_4$
13, R = 3,4-$(H_3CO)_2C_6H_3$
14, R = 4-(1-Piperidinyl)phenyl
15, R = 4-(4-Morpholinyl)phenyl
16, R = 2-Thienyl

17, R = Ph, R' = Me
18, R = Ph, R' = Et
19, R = Ph, R' = 1-Propyl
20, R = Ph, R' = Benzyl
21, R = 2-naphthyl, R' = Me
22, R = 2-naphthyl, R' = Et
23, R = 2-naphthyl, R' = 1-Propyl
24, R = 2-naphthyl, R' = Benzyl
25, R = 4-BrC_6H_4, R' = Me
26, R = 4-BrC_6H_4, R' = Et
27, R = 4-BrC_6H_4, R' = 1-Propyl
28, R = 4-ClC_6H_4, R' = Me
29, R = 4-ClC_6H_4, R' = Et
30, R = 4-ClC_6H_4, R' = 1-Propyl
31, R = 4-ClC_6H_4, R' = Benzyl
32, R = 2,4-$Cl_2C_6H_3$, R' = Me
33, R = 2,4-$Cl_2C_6H_3$, R' = Et
34, R = 2,4-$Cl_2C_6H_3$, R' = 1-Propyl
35, R = 2,4-$Cl_2C_6H_3$, R' = Benzyl
36, R = 4-FC_6H_4, R' = Me
37, R = 4-FC_6H_4, R' = 1-Propyl

Scheme 1. Synthetic pathway towards pyrano[3,2-*c*]pyridines.

38, R = 4-FC_6H_4, R' = Benzyl

39, R = 4-$H_3CC_6H_4$, R' = Me

40, R = 4-$H_3CC_6H_4$, R' = Et

41, R = 4-$H_3CC_6H_4$, R' = 1-Propyl

42, R = 4-$H_3CC_6H_4$, R' = Benzyl

43, R = 4-$H_3COC_6H_4$, R' = Me

44, R = 4-$H_3COC_6H_4$, R' = Et

45, R = 4-$H_3COC_6H_4$, R' = 1-Propyl

46, R = 4-$H_3COC_6H_4$, R' = Benzyl

47, R = 3,4-$(H_3CO)_2C_6H_3$, R' = Me

48, R = 3,4-$(H_3CO)_2C_6H_3$, R' = Et

49, R = 3,4-$(H_3CO)_2C_6H_3$, R' = 1-Propyl

50, R = 3,4-$(H_3CO)_2C_6H_3$, R' = Benzyl

51, R = 4-(1-Piperidinyl)phenyl, R' = Me

52, R = 4-(1-Piperidinyl)phenyl, R' = Et

53, R = 4-(4-Morpholinyl)phenyl, R' = Me

54, R = 4-(4-Morpholinyl)phenyl, R' = Et

55, R = 4-(4-Morpholinyl)phenyl, R' = Benzyl

56, R = 2-Thienyl, R' = Me

57, R = 2-Thienyl, R' = Et

Scheme 1. (*continued*).

4*a*,5,6,7,8,8*a*-hexahydro-8*a*-methoxy-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles **17**–**57** as the only products. The reaction was assumed to take place *via* nucleophilic attack of active methylene on 4-piperidone at the β-carbon of the unsaturated dinitrile system under the influence of the basic catalysts used. Cyclization due to methoxide nucleophilic attack at the carbonyl function and then interaction with the neighboring nitrile group furnished 2-amino-4-aryl-4*a*,5,6,7,8,8a-hexahydro-8*a*-methoxy-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (Scheme 1). Spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR) as well as elemental analysis values afford good support for the reported structures.

For example, compound **19** a representative of the synthesized pyranopyridine family, exhibited a strong stretching vibration at ν = 2185 cm^{-1} (C≡N) and a stretching vibration at ν = 3412, 3285 cm^{-1} (NH_2). The ^{1}H NMR spectrum of **19** exhibited methylene functions H_2C-5, H_2C-7 and H_2C-8 as diastereotropic protons at δ_H = 1.76, 2.24; 1.85, 2.72 and 1.58, 2.19, respectively. However, the methine *H*-4*a* was observed as a triplet at δ_H = 1.92. Additionally the methine *H*-4 appeared as a doublet at δ_H = 3.18. The ^{13}C NMR spectrum of compound **19** revealed the methylene carbons H_2C-5, H_2C-7 and H_2C-8 at δ_C = 59.7, 53.7 and 30.3, respectively. The methine carbons *HC*-4 and *HC*-4_a were observed at δ_C = 39.1 and 46.2, respectively and the quaternary carbons *C*-2, *C*-3, *C*-8*a* were located at δ_C = 162.1, 58.0 and 100.4, respectively. Finally, the methoxy and nitrile carbons appeared at δ_C = 48.8 and 121.8, respectively. For additional spectral data, see the Experimental Section. Single crystal X-ray studies of compounds **28**, **29** and **56** were reported in one of our publications exhibiting that the reaction produces only one stereoisomer. Also, it has been noticed that both the piperidinyl and pyranyl systems are distorted chair form configurations [9].

2.2. Bronchodilation activity

Bronchodilation properties of the synthesized pyrano[3,2-c] pyridine-3-carbonitriles **17**–**57** were investigated *in vitro* using isolated guinea pig tracheal rings pre-contracted with histamine according to the standard reported procedure [13] and compared with theophylline, that was used as a positive control (standard reference). The observed activity expressed as $IC_{50,}$ concentration of compounds necessary to reduce maximal histamine-induced contracture by 50% in guinea pig isolated tracheal rings is presented in Table 1 (Fig. 1 of Supplementary material).

The results indicate that all the compounds synthesized exhibit promising bronchodilation properties. Moreover, compounds **25** and **28** (IC_{50} = 7.9, 10.5 μM, respectively) revealed remarkable bronchodilatory potency comparable with that of theophylline (IC_{50} = 19.9 μM). Additionally, many synthesized pyrano[3,2-*c*] pyridine-3-carbonitrile analogs (namely, compounds **17, 26, 27, 29, 31, 32, 35, 36, 38, 39, 40, 47, 51, 52, 56** and **57**) showed bronchodilation activity enhanced relative to that of theophylline. In most cases (compound **51** is an exception) attachment of a methyl group to pyridinyl N-6 affords enhanced bronchodilation properties compared to *N*-ethyl analog.

Table 1
Concentrations of compounds **17**–**57** necessary to reduce maximal histamine-induced contracture by 50% (IC_{50}) in guinea pig isolated tracheal rings.

Entry	Compd.	R	R′	Potency (IC_{50}), μM
1	**17**	Ph	Me	19.8
2	**18**	Ph	Et	23.4
3	**19**	Ph	1-Propyl	20.7
4	**20**	Ph	Benzyl	22.6
5	**21**	2-Naphthyl	Me	24.2
6	**22**	2-Naphthyl	Et	28.3
7	**23**	2-Naphthyl	1-Propyl	37.1
8	**24**	2-Naphthyl	Benzyl	23.4
9	**25**	4-BrC_6H_4	Me	7.9
10	**26**	4-BrC_6H_4	Et	13.2
11	**27**	4-BrC_6H_4	1-Propyl	19.4
12	**28**	4-ClC_6H_4	Me	10.5
13	**29**	4-ClC_6H_4	Et	14.9
14	**30**	4-ClC_6H_4	1-Propyl	30.3
15	**31**	4-ClC_6H_4	Benzyl	18.5
16	**32**	2,4-$Cl_2C_6H_3$	Me	14.9
17	**33**	2,4-$Cl_2C_6H_3$	Et	27.1
18	**34**	2,4-$Cl_2C_6H_3$	1-Propyl	35.5
19	**35**	2,4-$Cl_2C_6H_3$	Benzyl	18.3
20	**36**	4-FC_6H_4	Me	19.4
21	**37**	4-FC_6H_4	1-Propyl	29.6
22	**38**	4-FC_6H_4	Benzyl	17.2
23	**39**	4-$H_3CC_6H_4$	Me	13.2
24	**40**	4-$H_3CC_6H_4$	Et	16.8
25	**41**	4-$H_3CC_6H_4$	1-Propyl	21.0
26	**42**	4-$H_3CC_6H_4$	Benzyl	27.1
27	**43**	4-$H_3COC_6H_4$	Me	23.1
28	**44**	4-$H_3COC_6H_4$	Et	25.5
29	**45**	4-$H_3COC_6H_4$	1-Propyl	21.3
30	**46**,	4-$H_3COC_6H_4$	Benzyl	23.1
31	**47**	3,4-$(H_3CO)_2C_6H_3$	Me	19.1
32	**48**	3,4-$(H_3CO)_2C_6H_3$	Et	23.2
33	**49**	3,4-$(H_3CO)_2C_6H_3$	1-Propyl	24.7
34	**50**	3,4-$(H_3CO)_2C_6H_3$	Benzyl	21.9
35	**51**	4-(1-Piperidinyl)phenyl	Me	19.0
36	**52**	4-(1-Piperidinyl)phenyl	Et	13.8
37	**53**	4-(4-Morpholinyl)phenyl	Me	20.2
38	**54**	4-(4-Morpholinyl)phenyl	Et	28.7
39	**55**	4-(4-Morpholinyl)phenyl	Benzyl	25.4
40	**56**	2-Thienyl	Me	13.8
41	**57**	2-Thienyl	Et	19.8
42	Theophylline	–	–	19.9

To afford a better understanding of the dependence of the observed pharmacological activity and determine the parameters controlling these properties, QSAR studies were applied utilizing Comprehensive Descriptors for Structural and Statistical Analysis (CODESSA-Pro).

2.3. QSAR study

2.3.1. Methodology

Data set of the bronchodilation properties of the synthesized analogs **17**–**57** were used in the present QSAR study. Compound structures were preliminary optimized using molecular mechanics (MM2) implemented in ChemBio Office 2012 (Chem3D Pro 13.0) and export to CODESSA-Pro where its included MOPAC, refined final geometry optimization. CODESSA-Pro calculated 783 constitutional, topological, geometrical, quantum chemical and electrostatic descriptors for the exported bio-active analogs.

2.3.2. Multi-linear modeling

Mathematical transformations of the bio-active agent property values were utilized for QSAR modeling including IC_{50}, $1/IC_{50}$, $\log(IC_{50})$ and $1/\log(IC_{50})$. BMLC (best multi-linear regression) was initiated stepwise to search for the best n-parameter regression equations, based on the highest R^2 (Squared correlation coefficient) and F (Fisher criteria) values. The QSAR models with up to 8 descriptors were generated (the maximum number allowed according to the 5:1 rule of thumb, the ratio between the data points and the number of descriptors). The statistical parameters including the square of the correlation coefficient (R^2), the leave-one-out squared cross-validated correlation coefficient (R^2cv), the Fisher criterion (F) and the variance (s^2) were used to select the best QSAR model (Table 2).

The best observed multi-linear QSAR model for $1/\log(IC_{50})$ is displayed in Fig. 1. It is seen that the model is statistically significant and the scatter is uniform, about one logarithmic unit. The descriptors by this observed multi-linear QSAR model are presented in Table 2 arranged based on their level of significance (t-criterion) in the following order: Average atom weight, LUMO + 1 energy, Shadow plane YZ, Max. PI–PI bond order, Number of aromatic bonds, Polarity parameter (Zefirov), Shadow plane ZX, and Max. total interaction for bond C–C.

The most important descriptor controlling the QSAR model given in Table 2 is Average atom weight, which is a constitutional descriptor, reflecting the chemical composition of a compound without any information about its molecular geometry or atom connectivity [14a]. The second important descriptor is the LUMO + 1 energy. Lowest unoccupied molecular orbital (LUMO) energy is one of the molecular orbital related descriptors and can be determined by equation (1) [14b]:

$$\varepsilon_{LUMO} = \left(\phi_{LUMO}|\widehat{F}|\phi_{LUMO}\right) \quad (1)$$

Table 2
Descriptor of the multi-linear QSAR model.

ID	X	ΔX	t	Descriptor name
0	−76.854	14.541	−5.285	Intercept
1	0.139	0.017	8.033	Average atom weight
2	0.546	0.075	7.304	LUMO + 1 energy
3	−0.010	0.002	−6.881	Shadow plane YZ
4	48.031	8.945	5.369	Max. PI–PI bond order
5	0.015	0.003	4.688	Number of aromatic bonds
6	−7.740	2.123	−3.646	Polarity parameter (Zefirov)
7	0.004	0.001	3.308	Shadow plane ZX
8	−0.562	0.225	−2.504	Max. total interaction for bond C–C

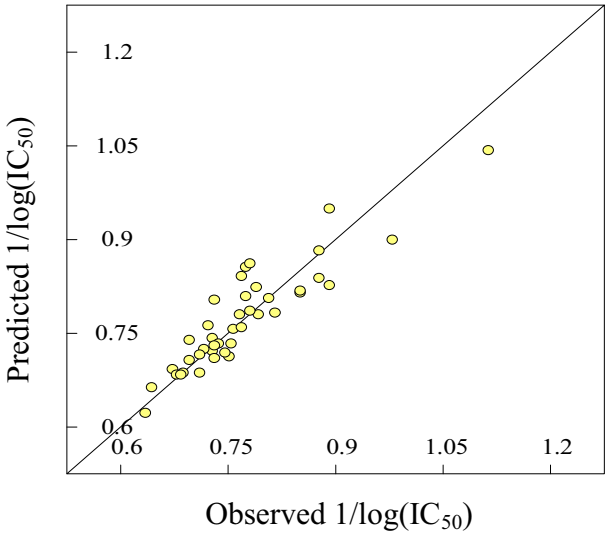


Fig. 1. QSAR multi-linear model plot of correlation representing the predicted vs observed $1/\log(IC_{50})$ "N (number of data points) = 41, n (number of descriptors) = 8, R^2 (squared correlation coefficient) = 0.824, R^2_{cv} (squared cross validation correlation) = 0.724, F (Fisher criterion) = 18.749, s^2 (variance) = 0.0018. Ranges: Observed (0.637–1.114), Predicted (0.621–1.041)".

where, $Ø_{lumo}$ = lowest unoccupied molecular orbital and F = Fock operator. LUMO + 1, similar to LUMO, is a good measure of electrophilicity of a compound. The Shadow plane YZ and Shadow plane ZX are geometrical descriptors reflecting molecular size. Most geometrical descriptors are calculated directly from the (x,y,z) coordinates and other quantities derived from the coordinates, e.g. interatomic distances or distances from a specified origin (e.g. the molecule bary-center) [14c]. Max. PI–PI bond order and number of aromatic bonds are molecular type descriptors both describing unsaturation and aromaticity. Polarity parameter (P) is a charge-related descriptor and can be determined by equation (2):

$$P = Q_{max} - Q_{min} \quad (2)$$

where Q_{max} is the most positive atomic partial charge in the molecule and Q_{min}, is the most negative atomic partial charge in the molecule [14d,e]. Max. total interaction for bond C–C is a semi-empirical descriptor which is a measure of the bond strength.

The predicted values (IC_{50}) by the QSAR model are given in Table 3. Most of the potent analogs revealed IC_{50} values close to the experimental values which suggests the model is statistically significant. Slight differences between the experimentally observed and predicted IC_{50} values were observed for compounds **37**, **38**, **48**, **55** and **56** (0.20–0.29 μM). However, the highest difference was observed for compounds **17**, **27**, **42**, **43**, **45** and **51** (5.44–4.18 μM). Most of these analogs are not potent compared to either the theophylline (standard reference) or our effective analogs (**25**, **28**). Thus, the model can be used for the predication of more effective bronchodilatory hits. Although the present QSAR study uses a short set of data points (41 compounds), homogeneity of the set (the same scaffold) may explain the success of this study.

3. Conclusion

In conclusion, the bronchodilatory active 4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles **17**–**57** were synthesized through a facile approach *via* reaction of 1-alkyl-4-piperidones **1**–**4** with ylidenemalononitriles **5**–**16** in methanol in the presence of sodium.

Table 3
Observed and predicated values of the synthesized compounds **17**–57 according to the multi-linear QSAR model.

Entry	Compd.	Observed IC_{50}, μM	Predicted IC_{50}, μM	Error
1	**17**	19.80	15.47	4.33
2	**18**	23.40	22.24	1.16
3	**19**	20.70	21.14	−0.44
4	**20**	22.60	23.15	−0.55
5	**21**	24.20	20.65	3.55
6	**22**	28.30	28.75	−0.45
7	**23**	37.10	40.66	−3.56
8	**24**	23.40	24.33	−0.93
9	**25**	7.90	9.13	−1.23
10	**26**	13.20	11.37	1.83
11	**27**	19.40	14.74	4.66
12	**28**	10.50	12.93	−2.43
13	**29**	14.90	16.92	−2.02
14	**30**	30.30	27.98	2.32
15	**31**	18.50	16.37	2.13
16	**32**	14.90	16.69	−1.79
17	**33**	27.10	26.01	1.09
18	**34**	35.50	32.36	3.14
19	**35**	18.30	19.13	−0.83
20	**36**	19.40	17.21	2.19
21	**37**	29.60	29.31	0.29
22	**38**	17.20	17.46	−0.26
23	**39**	13.20	16.31	−3.11
24	**40**	16.80	18.96	−2.16
25	**41**	21.00	23.16	−2.16
26	**42**	27.10	22.66	4.44
27	**43**	23.10	17.66	5.44
28	**44**	25.50	28.62	−3.12
29	**45**	21.30	25.48	−4.18
30	**46**,	23.10	25.86	−2.76
31	**47**	19.10	18.73	0.37
32	**48**	23.20	23.45	−0.25
33	**49**	24.70	24.16	0.54
34	**50**	21.90	24.72	−2.82
35	**51**	19.00	14.54	4.46
36	**52**	13.80	15.65	−1.85
37	**53**	20.20	19.18	1.02
38	**54**	28.70	29.01	−0.31
39	**55**	25.40	25.16	0.24
40	**56**	13.80	13.60	0.20
41	**57**	19.80	20.81	−1.01

Bronchodilation properties of the synthesized analogs **17**–**57** were investigated *in vitro* using isolated guinea pig tracheal rings pre-contracted with histamine according to the standard procedure. Most of the compounds synthesized exhibit promising bronchodilation properties. Moreover, compounds **25** and **28** (IC_{50} = 7.9, 10.5 μM, respectively) revealed remarkable bronchodilatory potency compared to that of theophylline (standard reference, IC_{50} = 19.9 μM). The use of CODESSA PRO software provided a robust QSAR model describing the bioactivity of 41 bronchodilatory active 4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles. Significance of the model can be attributed to the use in the present study of a homogenous data set. The satisfactory QSAR results also indicate that the experimental bio-assay data are internally consistent. This plus the surprisingly high activities of selected compounds **17**–**57** introduces a new, highly potent class of bronchodilators.

4. Experimental

Melting points were recorded on digital Electrothermal 9100 and Stuart SMP3 melting point instruments. IR spectra (KBr) were recorded on a Shimadzu FT-IR 8400S spectrophotometer. ^{1}H NMR spectra were recorded on Varian MERCURY 300BB (^{1}H: 300 MHz) and JEOL AS 500 (^{1}H: 500 MHz) spectrometers. ^{13}C NMR spectra were recorded on a JEOL AS 500 (^{13}C: 125 MHz) spectrometer. HRMS were recorded on Agilent Technology 6210 Time of Flight LC/MS spectrometer operating in the ESI mode. The starting compounds **5**–**16** were prepared according to the previously reported procedures [15].

*4.1. Synthesis of 6-alkyl-2-amino-4-aryl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4H-pyrano[3,2-c]pyridine-3-carbonitriles **17**–**57** (general procedure)*

A mixture of equimolar amounts of the appropriate **1**–**4** and the corresponding **5**–**16** (10 mmol) in methanol (25 ml) containing sodium (0.46 g, 20 mmol) was stirred at room temperature (20–25 °C) for 24 h. The separated solid was collected, washed with water and crystallized from a suitable solvent affording **17-57**.

*4.1.1. 2-Amino-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-methyl-4-phenyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**17**)*

Obtained from reaction of **1** and **5**. Colorless microcrystals from n-butanol, mp 253–255 °C (lit. mp 253–255 °C [9]), yield 2.0 g (67%).

*4.1.2. 2-Amino-6-ethyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-phenyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**18**)*

Obtained from reaction of **2** and **5**. Colorless microcrystals from n-butanol, mp 242–244 °C (lit. mp 242–244 °C [9]), yield 2.2 g (70%).

*4.1.3. 2-Amino-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-phenyl-6-(1-propyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**19**)*

Obtained from reaction of **3** and **5**. Colorless microcrystals from n-butanol, mp 231–233 °C, yield 2.6 g (80%). IR: ν_{max}/cm^{-1} 3412, 3285, 2185, 1643, 1607. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.67 (t, J = 7.3 Hz, 3H), 1.17–1.25 (m, 2H), 1.58 (t, J = 13.4 Hz, 1H), 1.76 (t, J = 13.0 Hz, 1H), 1.85 (t, J = 10.7 Hz, 1H), 1.92 (t, J = 11.5 Hz, 1H), 2.08 (br s, 2H), 2.19 (d, J = 7.7 Hz, 1H), 2.24 (d, J = 14.6 Hz, 1H), 2.72 (d, J = 10.7 Hz, 1H), 3.18 (d, J = 10.7 Hz, 1H), 3.24 (s, 3H), 6.35 (s, 2H), 7.15–7.30 (m, 5H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.1, 20.1, 30.3, 39.1, 46.2, 48.8, 49.4, 53.7, 58.0, 59.7, 100.4, 121.8, 127.5, 128.8, 128.9, 142.5, 162.1. Anal. Calcd. for $C_{19}H_{25}N_3O_2$ (327.43): C, 69.70; H, 7.70; N, 12.83. Found: C, 69.88; H, 8.02; N, 12.63.

*4.1.4. 2-Amino-6-benzyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-phenyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**20**)*

Obtained from reaction of **4** and **5**. Colorless microcrystals from n-butanol, mp 202–204 °C, yield 2.7 g (72%). IR: ν_{max}/cm^{-1} 3416, 3291, 2178, 1651, 1595. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.58 (td, J = 13.8, 3.8 Hz, 1H), 1.86 (td, J = 11.5, 3.8 Hz, 1H), 1.91–2.01 (m, 2H), 2.21 (d, J = 13.8 Hz, 1H), 2.30 (dd, J = 10.7, 3.1 Hz, 1H), 2.60 (d, J = 11.5 Hz, 1H), 3.20 (d, J = 10.7 Hz, 1H), 3.23 (s, 3H), 3.37 (br s, 1H), 3.42 (d, J = 13.0 Hz, 1H), 6.40 (s, 2H), 7.10–7.30 (m, 10H). ^{13}C NMR (125 Hz, DMSO-d_6): δ 30.2, 39.1, 46.1, 48.8, 49.0, 53.8, 58.0, 61.8, 100.3, 121.8, 127.4, 128.6, 128.8, 128.9, 129.2, 138.5, 142.5, 162.1. Anal. Calcd. for $C_{23}H_{25}N_3O_2$ (375.47): C, 73.58; H, 6.71; N, 11.19. Found: C, 73.42; H, 6.81; N, 11.08.

*4.1.5. 2-Amino-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-methyl-4-(2-naphthyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**21**)*

Obtained from reaction of **1** and **6**. Colorless microcrystals from n-butanol, mp 235–237 °C, yield 2.4 g (69%). IR: ν_{max}/cm^{-1} 3433, 3408, 3289, 2180, 1647, 1603. ^{1}H NMR (500 Mz, DMSO-d_6): δ 1.67 (t, J = 13.4 Hz, 1H), 1.88 (t, J = 10.0 Hz, 1H), 1.94–2.01 (m, 5H), 2.14 (d, J = 10.7 Hz, 1H), 2.26 (d, J = 12.2 Hz, 1H), 2.63 (d, J = 10.7 Hz, 1H), 3.28 (br s, 4H), 6.47 (s, 2H), 7.35–7.86 (m, 7H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 30.4, 39.3, 45.7, 45.9, 48.9, 52.0, 55.6, 58.0, 100.0, 121.8, 126.2, 126.7, 127.7, 128.1, 128.7, 132.9, 133.5, 140.1, 162.1. Anal. Calcd.

for $C_{21}H_{23}N_3O_2$ (349.44): C, 72.18; H, 6.63; N, 12.03. Found: C, 72.40; H, 6.76; N, 11.84.

*4.1.6. 2-Amino-6-ethyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-(2-naphthyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**22**)*

Obtained from reaction of **2** and **6**. Colorless microcrystals from n-butanol, mp 224–226 °C, yield 2.6 g (72%). IR: ν_{max}/cm^{-1} 3439, 3291, 2183, 1645, 1595. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.72 (t, J = 6.9 Hz, 3H), 1.63 (t, J = 13.0 Hz, 1H), 1.90–1.99 (m, 3H), 2.12–2.14 (m, 2H), 2.22 (d, J = 8.5 Hz, 1H), 2.27 (d, J = 13.8 Hz, 1H), 2.74 (d, J = 10.7 Hz, 1H), 3.27 (s, 3H), 3.39 (d, J = 10.7 Hz, 1H), 6.47 (s, 2H), 7.35–7.86 (m, 7H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.4, 30.3, 39.3, 45.9, 48.9, 51.4, 53.5, 58.0, 100.4, 121.9, 126.2, 126.7, 127.7, 128.1, 128.7, 132.9, 133.5, 140.1, 162.1. Anal. Calcd. for $C_{22}H_{25}N_3O_2$ (363.46): C, 72.70; H, 6.93; N, 11.56. Found: C, 72.98; H, 7.10; N, 11.55.

*4.1.7. 2-Amino-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-(2-naphthyl)-6-(1-propyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**23**)*

Obtained from reaction of **3** and **6**. Colorless microcrystals from n-butanol, mp 220–222 °C, yield 2.5 g (66%). IR: ν_{max}/cm^{-1} 3387, 3292, 2180, 1647, 1601. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.61 (br s, 3H), 1.14 (br s, 2H), 1.63 (br s, 1H), 1.94 (br s, 3H), 2.04 (br s, 2H), 2.24 (br d, 2H), 2.73 (br s, 1H), 3.25-3.29 (m, 4H), 6.44 (s, 2H), 7.36–7.86 (m, 7H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.1, 20.1, 30.4, 39.3, 45.9, 48.8, 49.3, 53.9, 58.0, 59.6, 100.4, 121.9, 126.2, 126.6, 127.7, 128.1, 128.7, 132.9, 133.5, 140.1, 162.1. Anal. Calcd. for $C_{23}H_{27}N_3O_2$ (377.49): C, 73.18; H, 7.21; N, 11.13. Found: C, 73.43; H, 7.50; N, 11.03.

*4.1.8. 2-Amino-6-benzyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-(2-naphthyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**24**)*

Obtained from reaction of **4** and **6**. Colorless microcrystals from n-butanol, mp 222–224 °C, yield 3.2 g (75%). IR: ν_{max}/cm^{-1} 3424, 3283, 2178, 1641, 1597. ^{1}H NMR (500 Mz, DMSO-d_6): δ 1.61 (t, J = 11.1 Hz, 1H), 1.94 (t, J = 11.8 Hz, 1H), 2.07–2.11 (m, 2H), 2.22 (d, J = 13.8 Hz, 1H), 2.35 (d, J = 7.7 Hz.1H), 2.58 (d, J = 10.7 Hz, 1H), 3.14 (d, J = 13.8 Hz, 1H), 3.42 (s, 5H), 6.47 (s, 2H), 7.08–7.85 (m, 12H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 30.2, 39.3, 45.9, 48.9, 54.1, 58.1, 61.8, 100.4, 121.9, 126.2, 126.6, 127.4, 127.7, 128.1, 128.5, 128.7, 129.3, 132.9, 133.5, 138.5, 140.1, 162.1. Anal. Calcd. for $C_{27}H_{27}N_3O_2$ (425.54): C, 76.21; H, 6.40; N, 9.87. Found: C, 76.23; H, 6.57; N, 9.79.

*4.1.9. 2-Amino-4-(4-bromophenyl)-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-methyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**25**)*

Obtained from reaction of **1** and **7**. Colorless microcrystals from n-butanol, mp 237–239 °C, yield 2.7 g (71%). IR: ν_{max}/cm^{-1} 3389, 2183, 1651, 1605. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.65 (td, J = 13.2, 4.1 Hz, 1H), 1.78–2.01 (m, 3H), 2.05 (s, 3H), 2.15 (dd, J = 16.1, 9.2 Hz, 1H), 2.26 (d, J = 13.8 Hz, 1H), 2.66 (d, J = 11.4 Hz, 1H), 3.22 (d, J = 10.2 Hz, 1H), 3.30 (s, 3H), 6.41 (s, 2H), 7.17 (d, J = 7.8 Hz, 2H), 7.51 (d, J = 7.8 Hz, 2H). Anal. Calcd. for $C_{17}H_{20}BrN_3O_2$ (378.27): C, 53.98; H, 5.33; N, 11.11. Found: C, 54.34; H, 5.41; N, 10.57.

*4.1.10. 2-Amino-4-(4-bromophenyl)-6-ethyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**26**)*

Obtained from reaction of **2** and **7**. Colorless microcrystals from n-butanol, mp 223–225 °C, yield 2.6 g (66%). IR: ν_{max}/cm^{-1} 3408, 3285, 2183, 1645, 1607. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.83 (t, J = 7.1 Hz, 3H), 1.62 (td, J = 13.2, 4.1 Hz, 1H), 1.80 (td, J = 10.8, 2.9 Hz, 1H), 1.86–1.99 (m, 2H), 2.18–2.30 (m, 4H), 2.77 (d, J = 11.1 Hz, 1H), 3.22 (d, J = 11.1 Hz, 1H), 3.29 (s, 3H), 6.40 (s, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H). Anal. Calcd. for $C_{18}H_{22}BrN_3O_2$ (392.30): C, 55.11; H, 5.65; N, 10.71. Found: C, 55.33; H, 5.74; N, 10.33.

*4.1.11. 2-Amino-4-(4-bromophenyl)-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-(1-propyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**27**)*

Obtained from reaction of **3** and **7**. Colorless microcrystals from n-butanol, mp 213–215 °C, yield 2.9 g (71%). IR: ν_{max}/cm^{-1} 3366, 2183, 1661, 1601. ^{1}H NMR (300 Mz, $CDCl_3$): δ 0.81 (t, J = 7.2 Hz, 3H), 1.38 (sextet, J = 6.9 Hz, 2H), 1.67 (br s, 1H), 1.83 (t, J = 11.6 Hz, 1H), 1.98–2.15 (m, 3H), 2.26 (t, J = 11.7 Hz, 2H), 2.44 (d, J = 6.3 Hz, 1H), 2.88 (d, J = 11.4 Hz, 1H), 3.31–3.34 (br d, 4H), 4.43 (s, 2H), 7.09 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H). Anal. Calcd. for $C_{19}H_{24}BrN_3O_2$ (406.33): C, 56.16; H, 5.95; N, 10.34. Found: C, 56.51; H, 6.05; N, 10.11.

*4.1.12. 2-Amino-4-(4-chlorophenyl)-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-methyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**28**)*

Obtained from reaction of **1** and **8**. Colorless microcrystals from n-butanol, mp 251–253 °C(lit. mp 251–253 °C [9]), yield 2.3 g (69%).

*4.1.13. 2-Amino-4-(4-chlorophenyl)-6-ethyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**29**)*

Obtained from reaction of **2** and **8**. Almost colorless microcrystals from n-butanol, mp 240–242 °C (lit. mp 240–242 °C [9]), yield 2.5 g (72%).

*4.1.14. 2-Amino-4-(4-chlorophenyl)-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-(1-propyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**30**)*

Obtained from reaction of **3** and **8**. Colorless microcrystals from n-butanol, mp 219–221 °C, yield 2.4 g (66%). IR: ν_{max}/cm^{-1} 3393, 3291, 2183, 1647, 1607. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 (t, J = 7.4 Hz, 3H), 1.32–1.44 (m, 2H), 1.68 (br s, 1H), 1.83 (t, J = 11.7 Hz, 1H), 1.98–2.15 (m, 2H), 2.23–2.32 (m, 3H), 2.44 (d, J = 7.8 Hz, 1H), 2.87 (d, J = 11.1 Hz, 1H), 3.338 (s, 3H), 3.34 (d, J = 10.8 Hz, 1H), 4.43 (s, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H). Anal. Calcd. for $C_{19}H_{24}ClN_3O_2$ (361.88): C, 63.06; H, 6.68; N, 11.61. Found: C, 63.08; H, 6.81; N, 11.45.

*4.1.15. 2-Amino-6-benzyl-4-(4-chlorophenyl)-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**31**)*

Obtained from reaction of **4** and **8**. Colorless microcrystals from n-butanol, mp 182–184 °C, yield 3.0 g (73%). IR: ν_{max}/cm^{-1} 3408, 3348, 2181, 1643, 1601. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.74 (td, J = 13.4, 3.9 Hz, 1H), 1.99–2.25 (m, 3H), 2.50 (dd, J = 10.5, 2.4 Hz, 1H), 2.73 (d, J = 11.7 Hz, 1H), 3.26 (d, J = 13.2 Hz, 1H), 3.32 (br s, 4H), 3.37 (d, J = 10.8 Hz, 1H), 3.61 (d, J = 13.2 Hz, 1H), 4.44 (s, 2H), 7.13–7.37 (m, 9H). Anal. Calcd. for $C_{23}H_{24}ClN_3O_2$ (409.92): C, 67.39; H, 5.90; N, 10.25. Found: C, 67.78; H, 6.17; N, 10.33.

*4.1.16. 2-Amino-4-(2,4-dichlorophenyl)-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-methyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**32**)*

Obtained from reaction of **1** and **9**. Colorless microcrystals from n-butanol, mp 224–226 °C, yield 2.4 g (65%). IR: ν_{max}/cm^{-1} 3402, 3298, 2185, 1653, 1605. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.64 (td, J = 13.8, 3.9 Hz, 1H), 1.85–1.97 (m, 3H), 2.02 (s, 3H), 2.14 (d, J = 6.2 Hz, 1H), 2.24 (d, J = 13.8 Hz, 1H), 2.63 (d, J = 11.5 Hz, 1H), 3.26 (s, 3H), 3.87 (d, J = 10.7 Hz, 1H), 6.50 (s, 2H), 7.37–7.54 (m, 3H). ^{13}C NMR (125 Hz, DMSO-d_6): δ 30.2, 34.0, 45.7, 46.5, 48.9, 51.9, 55.0, 56.6, 100.0, 121.3, 128.7, 128.9, 131.5, 132.5, 135.3, 139.1, 162.4. Anal. Calcd. for $C_{17}H_{19}Cl_2N_3O_2$ (368.27): C, 55.45; H, 5.20; N, 11.41. Found: C, 55.41; H, 5.26; N, 11.06.

*4.1.17. 2-Amino-4-(2,4-dichlorophenyl)-6-ethyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**33**)*

Obtained from reaction of **2** and **9**. Colorless microcrystals from n-butanol, mp 239–241 °C, yield 2.3 g (60%). IR: ν_{max}/cm^{-1} 3445, 3289, 2185, 1645, 1636, 1593. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.79 (br s, 3H), 1.61 (br s, 1H), 1.88–1.95 (m, 3H), 2.21 (br s, 4H), 2.74 (br s, 1H), 3.24 (s, 3H), 3.87 (br s, 1H), 6.39 (s, 2H), 7.36–7.49 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.4, 30.2, 34.1, 46.6, 48.9, 51.4, 52.9, 56.7, 100.4, 121.3, 128.6, 128.9, 131.4, 132.5, 135.3, 139.1, 162.4. Anal. Calcd. for $C_{18}H_{21}Cl_2N_3O_2$ (382.29): C, 56.55; H, 5.54; N, 10.99. Found: C, 56.87; H, 5.67; N, 10.82.

*4.1.18. 2-Amino-4-(2,4-dichlorophenyl)-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-(1-propyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**34**)*

Obtained from reaction of **3** and **9**. Colorless microcrystals from n-butanol, mp 210–212 °C, yield 2.6 g (66%). IR: ν_{max}/cm^{-1} 3335, 3294, 2183, 1643, 1601. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, J = 7.4 Hz, 3H), 1.39 (sextet, J = 7.2 Hz, 2H), 1.80 (td, J = 13.5, 4.2 Hz, 1H), 1.95 (td, J = 11.0, 3.6 Hz, 1H), 2.07–2.21 (m, 2H), 2.24–2.34 (m, 3H), 2.43 (dd, J = 11.4, 2.7 Hz, 1H), 2.86 (d, J = 11.1 Hz, 1H), 3.36 (s, 3H), 4.11 (d, J = 11.4 Hz, 1H), 4.46 (s, 2H), 7.28 (br s, 2H), 7.38 (s, 1H, arom. H). ^{13}C NMR (125 Hz, DMSO-d_6): δ 11.9, 20.1, 30.2, 33.3, 47.0, 48.9, 49.2, 53.0, 60.0, 60.4, 101.0, 120.4, 128.1, 129.2, 130.3, 133.4, 135.6, 137.3, 161.3. Anal. Calcd. for $C_{19}H_{23}Cl_2N_3O_2$ (396.32): C, 57.58; H, 5.85; N, 10.60. Found: C, 57.50; H, 5.93; N, 10.26.

*4.1.19. 2-Amino-6-benzyl-4-(2,4-dichlorophenyl)-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**35**)*

Obtained from reaction of **4** and **9**. Colorless microcrystals from n-butanol, mp 234–236 °C, yield 2.9 g (65%). IR: ν_{max}/cm^{-1} 3447, 3393, 3287, 2185, 1647, 1595. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.63 (td, J = 13.4, 4.2 Hz, 1H), 1.93–2.13 (m, 3H), 2.24–2.33 (m, 2H), 2.65 (d, J = 11.4 Hz, 1H), 3.26–3.32 (m, 4H), 3.51 (d, J = 12.9 Hz, 1H), 3.90 (d, J = 11.1 Hz, 1H), 6.49 (s, 2H), 7.14–7.54 (m, 8H). Anal. Calcd. for $C_{23}H_{23}Cl_2N_3O_2$ (444.36): C, 62.17; H, 5.22; N, 9.46. Found: C, 62.15; H, 5.35; N, 9.01.

*4.1.20. 2-Amino-4-(4-fluorophenyl)-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-methyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**36**)*

Obtained from reaction of **1** and **10**. Colorless microcrystals from n-butanol, mp 246–248 °C (lit. mp 246–248 °C [9]), yield 2.2 g (69%).

*4.1.21. 2-Amino-4-(4-fluorophenyl)-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-(1-propyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**37**)*

Obtained from reaction of **3** and **10**. Colorless microcrystals from n-butanol, mp 231–233 °C, yield 2.7 g (78%). IR: ν_{max}/cm^{-1} 3397, 3289, 2183, 1645, 1612. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.72 (t, J = 7.4 Hz, 3H), 1.18–1.31 (m, 2H), 1.62 (td, J = 13.2, 4.1 Hz, 1H), 1.79 (td, 1H, J = 11.1, 3.6 Hz), 1.85–2.00 (m, 2H), 2.13 (t, J = 7.5 Hz, 2H), 2.24 (t, J = 13.7 Hz, 1H), 2.76 (d, J = 11.1 Hz, 1H), 3.24 (d, J = 10.5 Hz, 1H), 3.27 (br s, 4H), 6.37 (s, 2H), 7.10–7.26 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.1, 20.1, 30.3, 38.3, 46.1, 48.8, 49.4, 53.6, 57.8, 59.6, 100.4, 115.6, 115.7, 121.7, 130.59, 130.6, 138.6, 160.7, 162.1, 162.6. Anal. Calcd. for $C_{19}H_{24}FN_3O_2$ (345.42): C, 66.07; H, 7.00; N, 12.16. Found: C, 65.90; H, 7.50; N, 11.76.

*4.1.22. 2-Amino-6-benzyl-4-(4-fluorophenyl)-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**38**)*

Obtained from reaction of **4** and **10**. Colorless microcrystals from n-butanol, mp 186–188 °C, yield 3.0 g (76%). IR: ν_{max}/cm^{-1} 3404, 3287, 2183, 1643, 1607. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.58 (t, J = 13.4 Hz, 1H), 1.84–1.86 (m, 1H), 1.97 (br s, 2H), 2.21 (d, J = 13.8 Hz, 1H), 2.27 (d, J = 7.7 Hz, 1H), 2.60 (d, J = 10.7 Hz, 1H), 3.20–3.25 (m, 5H), 3.44 (d, J = 13.0 Hz, 1H), 6.41 (s, 2H), 7.07–7.19 (m, 9H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 30.1, 38.3, 46.0, 48.8, 49.0, 53.6, 57.8, 61.7, 100.3, 115.5, 115.7, 121.7, 127.4, 128.6, 129.3, 130.7, 138.6, 162.0. Anal. Calcd. for $C_{23}H_{24}FN_3O_2$ (393.47): C, 70.21; H, 6.15; N, 10.68. Found: C, 70.06; H, 6.30; N, 10.58.

*4.1.23. 2-Amino-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-methyl-4-(4-methylphenyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**39**)*

Obtained from reaction of **1** and **11**. Colorless microcrystals from n-butanol, mp 238–240 °C (lit. mp 238–240 °C [9]), yield 2.3 g (73%).

*4.1.24. 2-Amino-6-ethyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-(4-methylphenyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**40**)*

Obtained from reaction of **2** and **11**. Colorless microcrystals from n-butanol, mp 234–236 °C, yield 2.2 g (67%). IR: ν_{max}/cm^{-1} 3416, 3287, 2180, 1645, 1605. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, J = 7.2 Hz, 3H), 1.81 (td, J = 13.4, 4.1 Hz, 1H), 1.94–2.12 (m, 3H), 2.26–2.43 (m, 6H), 2.49 (d, J = 6.6 Hz, 1H), 2.88 (d, J = 11.4 Hz, 1H), 3.29–3.34 (m, 4H), 4.39 (s, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H). HR-MS (ESI): m/z 328.2029 $[M + H]^+$; Calcd. for $C_{19}H_{25}N_3O_2$+H, 328.2025.

*4.1.25. 2-Amino-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-(4-methylphenyl)-6-(1-propyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**41**)*

Obtained from reaction of **3** and **11**. Colorless microcrystals from n-butanol, mp 220–222 °C, yield 2.1 g (62%). IR: ν_{max}/cm^{-1} 3420, 3387, 3291, 2180, 1643, 1603. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80 (t, J = 7.5 Hz, 3H), 1.31–1.41 (m, 2H), 1.79 (td, 1H, J = 13.4, 4.2 Hz), 1.94–2.13 (m, 3H), 2.18–2.33 (m, 6H), 2.47 (d, J = 6.6 HZ, 1H), 2.85 (d, J = 11.4 Hz, 1H), 3.29–3.33 (m, 4H), 4.38 (s, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.9, 20.1, 21.2, 30.3, 38.0, 45.8, 48.8, 49.2, 53.7, 60.0, 62.1, 101.1, 120.9, 128.3, 129.4, 136.9, 137.4, 160.7. HR-MS (ESI): m/z 342.2178 $[M + H]^+$; Calcd. for $C_{20}H_{27}N_3O_2$+H, 342.2182.

*4.1.26. 2-Amino-6-benzyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-(4-methylphenyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**42**)*

Obtained from reaction of **4** and **11**. Colorless microcrystals from n-butanol, mp 196–198 °C, yield 2.8 g (72%). IR: ν_{max}/cm^{-1} 3426, 3397, 3289, 2181, 1641, 1599. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.74 (br s, 1H), 2.02 (t, J = 11.3 Hz, 1H), 2.12–2.24 (m, 3H), 2.33 (s, 3H), 2.56 (d, J = 10.8 Hz, 1H), 2.71 (d, J = 11.1 Hz, 1H), 3.23 (d, J = 13.2 Hz, 1H), 3.32 (s, 3H),3.34 (d, J = 11.4 Hz, 1H), 3.64 (d, J = 13.2 Hz, 1H), 4.37 (s, 2H), 7.08–7.29 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 30.1, 38.0, 46.0, 48.3, 48.8, 54.3, 62.0, 62.2, 101.1, 120.9, 127.2, 128.4, 129.1, 129.5, 136.9, 137.5, 138.0, 160.7. Anal. Calcd. for $C_{24}H_{27}N_3O_2$ (389.50): C, 74.01; H, 6.99; N, 10.79. Found: C, 73.96; H, 7.31; N, 10.57.

*4.1.27. 2-Amino-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-(4-methoxyphenyl)-6-methyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**43**)*

Obtained from reaction of **1** and **12**. Colorless microcrystals from n-butanol, mp 228–230 °C (lit. mp 228–230 °C [9]), yield 2.2 g (67%).

*4.1.28. 2-Amino-6-ethyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-(4-methoxyphenyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**44**)*

Obtained from reaction of **2** and **12**. Colorless microcrystals from n-butanol, mp 207–208 °C (lit. mp 207–208 °C [9]), yield 2.4 g (70%).

*4.1.29. 2-Amino-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-(4-methoxyphenyl)-6-(1-propyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**45**)*

Obtained from reaction of **3** and **12**. Colorless microcrystals from n-butanol, mp 179–181 °C, yield 2.2 g (62%). IR: ν_{max}/cm^{-1} 3412, 3292, 2181, 1643, 1612. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.77 (t, J = 7.3 Hz, 3H), 1.30–1.37 (m, 2H), 1.76 (t, J = 11.5 Hz, 1H), 1.92–1.96 (m, 2H), 2.05 (t, J = 11.5 Hz, 1H), 2.19–2.26 (m, 3H), 2.43 (d, J = 6.1 Hz, 1H), 2.83 (d, J = 11.5 Hz, 1H), 3.26–3.32 (m, 4H), 3.77 (s, 3H), 4.46 (s, 2H), 6.83 (d, J = 9.2 Hz, 2H), 7.08 (d, J = 9.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.9, 20.1, 30.2, 37.6, 45.9, 48.8, 49.3, 53.6, 55.3, 60.0, 62.1, 101.0, 114.1, 120.9, 129.4, 132.5, 158.8, 160.6. Anal. Calcd. for $C_{20}H_{27}N_3O_3$ (357.46): C, 67.20; H, 7.61; N, 11.76. Found: C, 67.23; H, 8.06; N, 11.75.

*4.1.30. 2-Amino-6-benzyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-(4-methoxyphenyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**46**)*

Obtained from reaction of **4** and **12**. Colorless microcrystals from n-butanol, mp 202–204 °C, yield 3.2 g (79%). IR: ν_{max}/cm^{-1} 3412, 3285, 2185, 1643, 1607. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.59 (td, J = 13.4, 4.2 Hz, 1H), 1.84 (td, J = 11.1, 3.8 Hz, 1H), 1.94–2.04 (m, 2H), 2.24 (d, J = 13.8 Hz, 1H), 2.35 (dd, J = 10.7, 3.2 Hz, 1H), 2.62 (d, J = 11.1 Hz, 1H), 3.16 (d, J = 11.1 Hz, 1H), 3.25 (d, J = 13.20 Hz, 1H), 3.254 (s, 3H), 3.49 (d, J = 13.2 Hz, 1H), 3.73 (s, 3H), 6.30 (s, 2H), 6.84–7.26 (m, 9H). Anal. Calcd. for $C_{24}H_{27}N_3O_3$ (405.50): C, 71.09; H, 6.71; N, 10.36. Found: C, 71.25; H, 7.06; N, 10.28.

*4.1.31. 2-Amino-4-(3,4-dimethoxyphenyl)-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-methyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**47**)*

Obtained from reaction of **1** and **13**. Colorless microcrystals from n-butanol, mp 215–217 °C, yield 2.3 g (64%). IR: ν_{max}/cm^{-1} 3426, 3325, 2189, 1655, 1599. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.62 (br s, 1H), 1.80 (br s, 2H), 1.94 (br s, 1H), 2.02 (s, 3H), 2.15 (br s, 1H), 2.22 (d, J = 13.8 Hz, 1H), 2.63 (br s, 1H), 3.12 (br s, 1H), 3.23 (s, 3H), 3.70 (s, 6H), 6.32 (s, 2H), 6.67 (d, J = 6.9 Hz, 1H), 6.72 (s, 1H), 6.84 (d, J = 7.6 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 30.3, 38.6, 45.8, 45.9, 48.7, 52.0, 55.6, 55.9, 56.0, 58.3, 100.0, 112.0, 121.0, 121.8, 134.7, 148.2, 149.2, 161.9. Anal. Calcd. for $C_{19}H_{25}N_3O_4$ (359.43): C, 63.49; H, 7.01; N, 11.69. Found: C, 63.58; H, 7.41; N, 11.47.

*4.1.32. 2-Amino-4-(3,4-dimethoxyphenyl)-6-ethyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**48**)*

Obtained from reaction of **2** and **13**. Colorless microcrystals from ethanol, mp 221–223 °C, yield 2.1 g (56%). IR: ν_{max}/cm^{-1} 3431, 3291, 2185, 1643, 1595. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, J = 7.2 Hz, 3H), 1.80 (td, J = 13.4, 4.2 Hz, 1H), 1.95–2.12 (m, 3H), 2.26–2.43 (m, 3H), 2.49(d, = 6.9 Hz, 1H), 2.88 (d, J = 11.1 Hz, 1H), 3.30 (d, J = 10.8 Hz, 1H), 3.33 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.42 (s, 2H), 6.69–6.82 (m, 3H). Anal. Calcd. for $C_{20}H_{27}N_3O_4$ (373.46): C, 64.32; H, 7.29; N, 11.25. Found: C, 64.45; H, 7.68; N, 11.06.

*4.1.33. 2-Amino-4-(3,4-dimethoxyphenyl)-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-(1-propyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**49**)*

Obtained from reaction of **3** and **13**. Colorless microcrystals from n-butanol, mp 195–197 °C, yield 2.5 g (65%). IR: ν_{max}/cm^{-1} 3414, 3327, 2183, 1651, 1597. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.69 (t, J = 7.3 Hz, 3H), 1.20–1.25 (m, 2H), 1.58 (td, J = 13.8, 3.9 Hz, 1H), 1.77–1.91 (m, 3H), 2.09 (t, J = 7.3 Hz, 2H), 2.24 (br s, 2H), 2.73 (d, J = 10.7 Hz, 1H), 3.13 (d, J = 10.7 Hz, 1H), 3.23 (s, 3H), 3.69 (s, 3H), 3.70 (s, 3H), 6.31 (s, 2H), 6.67 (d, J = 7.7 Hz, 1H), 6.72 (s, 1H), 6.84 (d, J = 7.6 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.2, 20.1, 30.3, 38.7, 46.0, 48.7, 49.3, 53.9, 55.9, 56.0, 58.3, 59.7, 100.4, 112.0, 121.0, 121.8, 134.7, 148.2, 149.1, 162.0. Anal. Calcd. for $C_{21}H_{29}N_3O_4$ (387.48): C, 65.10; H, 7.54; N, 10.84. Found: C, 65.11; H, 8.02; N, 10.43.

*4.1.34. 2-Amino-6-benzyl-4-(3,4-dimethoxyphenyl)-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**50**)*

Obtained from reaction of **4** and **13**. Colorless microcrystals from methanol, mp 175–177 °C, yield 2.6 g (60%). IR: ν_{max}/cm^{-1} 3441, 3287, 2180, 1645, 1585. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.58 (br s, 1H), 1.87 (br s, 1H), 1.94–1.98 (m, 2H), 2.19 (br s, 1H), 2.37 (br s, 1H), 2.59 (br s, 1H), 3.22 (br s, 4H), 3.45 (br s, 2H), 3.67 (s, 6H), 6.36 (s, 2H), 6.66–7.20 (m, 8H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 30.2, 38.7, 46.0, 48.7, 49.0, 53.9, 55.9, 56.0, 58.3, 61.9, 100.4, 112.1, 120.9, 121.9, 127.4, 128.6, 129.3, 134.6, 138.5, 148.2, 149.1, 162.0. Anal. Calcd. for $C_{25}H_{29}N_3O_4$ (435.53): C, 68.95; H, 6.71; N, 9.65. Found: C, 68.72; H, 7.00; N, 9.41.

*4.1.35. 2-Amino-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-methyl-4-[4-(1-piperidinyl)phenyl]-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**51**)*

Obtained from reaction of **1** and **14**. Yellow microcrystals from methanol, mp 238–240 °C (lit. mp 238–240 °C [9]), yield 2.5 g (65%).

*4.1.36. 2-Amino-6-ethyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-[4-(1-piperidinyl)phenyl]-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**52**)*

Obtained from reaction of **2** and **14**. Yellow microcrystals from n-butanol, mp 231–233 °C (lit. mp 231–233 °C [9]), yield 2.3 g (58%).

*4.1.37. 2-Amino-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-methyl-4-[4-(4-morpholinyl)phenyl]-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**53**)*

Obtained from reaction of **1** and **15**. Pale yellow microcrystals from methanol, mp 241–243 °C (lit. mp 241–243 °C [9]), yield 2.3 g (60%).

*4.1.38. 2-Amino-6-ethyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-[4-(4-morpholinyl)phenyl]-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**54**)*

Obtained from reaction of **2** and **15**. Yellow microcrystals from n-butanol, mp 240–242 °C (lit. mp 240–242 °C [9]), yield 2.7 g (68%).

*4.1.39. 2-Amino-6-benzyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-[4-(4-morpholinyl)phenyl]-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**55**)*

Obtained from reaction of **4** and **15**. Pale yellow microcrystals from n-butanol, mp 222–224 °C, yield 3.7 g (80%). IR: ν_{max}/cm^{-1} 3466, 3339, 2183, 1647, 1587. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72 (br s, 1H), 2.01 (br t, 1H), 2.10-2.23 (m, 3H), 2.57 (d, J = 7.5 Hz, 1H), 2.71 (d, J = 9.9 Hz, 1H), 3.16 (t, J = 4.7 Hz, 4H), 3.23 (d, J = 12.3 Hz, 1H), 3.31 (d, J = 10.8 Hz, 1H), 3.32 (s, 3H), 3.64 (d, J = 12.3 Hz, 1H), 3.86 (t, J = 4.8 Hz, 4H), 4.37 (s, 2H), 6.86–7.29 (m, 9H). Anal. Calcd. for $C_{27}H_{32}N_4O_3$ (460.58): C, 70.41; H, 7.00; N, 12.16. Found: C, 70.16; H, 7.41; N, 11.85.

*4.1.40. 2-Amino-4a,5,6,7,8,8a-hexahydro-8a-methoxy-6-methyl-4-(2-thienyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**56**)*

Obtained from reaction of **1** and **16**. Colorless microcrystals from n-butanol, mp 245–247 °C (lit. mp 245–247 °C [9]), yield 2.1 g (69%).

*4.1.41. 2-Amino-6-ethyl-4a,5,6,7,8,8a-hexahydro-8a-methoxy-4-(2-thienyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**57**)*

Obtained from reaction of **2** and **16**. Almost colorless microcrystals from n-butanol, mp 228–230 °C (lit. mp 228–230 °C [9]), yield 2.3 g (72%).

4.2. Bronchodilation properties screening

The bronchodilation activity screening procedures were carried out according to the reported techniques [13] by testing the effects of the synthesized pyrano[3,2-*c*]pyridine-3-carbonitrile derivatives (**17**–**57**) on isolated guinea pig tracheal rings (350–400 g). The tracheae were quickly dissected from sacrificed guinea pigs and placed in a Petri dish containing physiological salt solution. The tracheae were cleaned of adherent connective tissues as much as possible and cut into rings of 2–3 mm length and each ring was placed in a vertical chamber "10 ml jacketed automatic multichamber organ bath system (Model no. ML870B6/C, Panlab, Spain)" filled with Krebs solution composed of (in mM): NaCl, 118.0; KCl, 4.7; $NaHCO_3$, 25.0; $CaCl_2$, 1.8; NaH_2PO_4, 1.2; $MgSO_4$, 1.2; glucose, 11.0 and oxygenated with bubbles of carbogen gas (95% O_2/5% CO_2) at 37 ± 0.5 °C. Each trachea ring was mounted between two stainless steel hooks. The lower hook was fixed between two plates, while the upper one was attached to a force displacement transducer (Model no. MLT0201, Panlab, Spain) connected to an amplifier (PowerLab, AD Instruments Pty. Ltd.) in turn connected to a computer. The Chart for windows (v 3.4) software was used to record and elaborate data. Preparations were stabilized under 1 g resting tension during 1 h and then the contracture response to histamine (10^{-6} M) was measured before and after exposure to increasing concentrations of the tested synthesized compounds. The tested compounds were dissolved in dimethylsulfoxide (DMSO) as stock solution (10 ml of 10^{-3} M). Control experiments were performed in the presence of DMSO alone, at the same concentrations as those used with the tested derivatives, which demonstrated that the solvent did not affect the contractile response of isolated trachea. The mean of three successive runs were used in each case to extract the experimental data. The observed bronchodilation activity screening data are reported (Table 1) and the potency (IC_{50}, concentration necessary for 50% reduction of maximal histamine induced contracture) was determined.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.12.032

References

[1] W.-J. Shan, L. Huang, Q. Zhou, H.-L. Jiang, Z.-H. Luo, K.-f. Lai, X.-S. Li, Bioorg. Med. Chem. Lett. 22 (2012) 1523–1526.
[2] P.J. Barnes, Nat. Rev. Immunol. 8 (2008) 183–192.
[3] P.J. Barnes, Allergy Clin. Immunol. 102 (1998) 531–535.
[4] H.A. Boushey, J. Allergy Clin. Immunol. 102 (1998) S5.
[5] P.A. Procopiou, V.J. Barrett, A.J. Ford, B.E. Looker, G.E. Lunniss, D. Needham, C.E. Smith, G. Somers, Bioorg. Med. Chem. 19 (2011) 6026–6032.
[6] A.D. Hughes, K.H. Chin, S.L. Dunham, J.R. Jasper, K.E. King, T.W. Lee, M. Mammen, J. Martin, T. Steinfeld, Bioorg. Med. Chem. Lett. 21 (2011) 1354–1358.
[7] (a) R.F. George, N.S.M. Ismail, J. Stawinski, A.S. Girgis, Eur. J. Med. Chem. 68 (2013) 339–351;
(b) A.M. Moustafa, A.S. Girgis, S.M. Shalaby, E.R.T. Tiekink, Acta Crystallogr. Sect. E: Struct. Rep. Online E68 (2012) o2197–o2198;
(c) A.S. Girgis, S.R. Tala, P.V. Oliferenko, A.A. Oliferenko, A.R. Katritzky, Eur. J. Med. Chem. 50 (2012) 1–8;
(d) A.S. Girgis, J. Stawinski, N.S.M. Ismail, H. Farag, Eur. J. Med. Chem. 47 (2012) 312–322;
(e) A.S. Girgis, H. Farag, N.S.M. Ismail, R.F. George, Eur. J. Med. Chem. 46 (2011) 4964–4969;
(f) A.R. Katritzky, A.S. Girgis, S. Slavov, S.R. Tala, I. Stoyanova-Slavova, Eur. J. Med. Chem. 45 (2010) 5183–5199;
(g) A.S. Girgis, F.F. Barsoum, A. Samir, Eur. J. Med. Chem. 44 (2009) 2447–2451;
(h) F.F. Barsoum, A.S. Girgis, Eur. J. Med. Chem. 44 (2009) 2172–2177;
(i) A.S. Girgis, F.F. Barsoum, Eur. J. Med. Chem. 44 (2009) 1972–1977;
(j) A.S. Girgis, Eur. J. Med. Chem. 44 (2009) 1257–1264;
(k) A.S. Girgis, Eur. J. Med. Chem. 44 (2009) 91–100;
(l) A.S. Girgis, Eur. J. Med. Chem. 43 (2008) 2116–2121;
(m) A.S. Girgis, N. Mishriky, M. Ellithey, H.M. Hosni, H. Farag, Bioorg. Med. Chem. 15 (2007) 2403–2413;
(n) A.S. Girgis, M. Ellithey, Bioorg. Med. Chem. 14 (2006) 8527–8532;
(o) A.S. Girgis, H.M. Hosni, F.F. Barsoum, Bioorg. Med. Chem. 14 (2006) 4466–4476;
(p) F.F. Barsoum, H.M. Hosni, A.S. Girgis, Bioorg. Med. Chem. 14 (2006) 3929–3937;
(q) A.S. Girgis, A. Kalmouch, H.M. Hosni, Amino Acids 26 (2004) 139–146.
[8] (a) Z.M. Nofal, A.M. Srour, W.I. El-Eraky, D.O. Saleh, A.S. Girgis, Eur. J. Med. Chem. 63 (2013) 14–21;
(b) A.S. Girgis, N.S.M. Ismail, H. Farag, W.I. El-Eraky, D.O. Saleh, S.R. Tala, A.R. Katritzky, Eur. J. Med. Chem. 45 (2010) 4229–4238;
(c) A.S. Girgis, N. Mishriky, A.M. Farag, W.I. El-Eraky, H. Farag, Eur. J. Med. Chem. 43 (2008) 1818–1827;
(d) A.S. Girgis, A. Kalmouch, M. Ellithey, Bioorg. Med. Chem. 14 (2006) 8488–8494;
(e) A.S. Girgis, H.M. Hosni, F.F. Barsoum, A.M.M. Amer, I.S. Ahmed Farag, Boll. Chim. Farm. 143 (2004) 365–375.
[9] A.S. Girgis, N.S.M. Ismail, H. Farag, Eur. J. Med. Chem. 46 (2011) 2397–2407.
[10] T. Yamanaka, M. Yasumoto, T. Nakajima, O. Yaoka, Jpn. Kokai Tokkyo Koho JP 04,282,353 (92,282,353) (Cl. C07C239/20), 7 Oct. 1992, Chem. Abstr. 118 (1993) 169097.
[11] M. Baumgarth, R. Gericke, I. Lues, J. De Peyer, R. Bergmann, Eur. Pat. Appl. EP 308,792 (Cl. C07D491/04), 29 Mar. 1989; Chem. Abstr. 111 (1989) 97213.
[12] J.M. Evans, G. Stemp, F. Cassidy, Eur. Pat. Appl. EP 205,292 (Cl. C07D491/04), 17 Dec. 1986, Chem. Abstr. 106 (1987) 213921.
[13] R.I. Ozolua, C.J. Eboka, C.N. Duru, D.O. Uwaya, Niger. J. Physiol. Sci. 25 (2010) 149–157.
[14] (a) http://www.talete.mi.it/help/dproperties_help/constitutional_descriptors.htm.
(b) http://www.codessa-pro.com/descriptors/MO/LUMO.htm.
(c) http://michem.disat.unimib.it/chm/download/materiale/geometrical_descriptors.pdf.
(d) http://www.codessa-pro.com/descriptors/electrostatic/polarity.htm. (e) K. Ośmialowski, J. Halkiewicz, A. Radecki, R. Kaliszan, J. Chromatogr. 346 (1985) 53–60.
[15] (a) B.B. Corson, R.W. Stoughton, J. Am. Chem. Soc. 50 (1928) 2825–2837;
(b) H.G. Sturz, C.R. Noller, J. Am. Chem. Soc. 71 (1949) 2949;
(c) M.A. Weinberger, R.M. Heggie, H.L. Holmes, Can. J. Chem. 43 (1965) 2585–2593;
(d) L. Horner, K. Klüpfel, Liebigs Ann. Chem. 591 (1955) 69–98;
(e) J.S.A. Brunskill, A. De, G.M.F. Vas, Synth. Commun. 8 (1978) 1–7;
(f) L.C.W. Chang, J.K.v.F.D. Künzel, T. Mulder-Krieger, R.F. Spanjersberg, S.F. Roerink, G. van den Hout, M.W. Beukers, J. Brussee, A.P. IJzerman, J. Med. Chem. 48 (2005) 2045–2053;
(g) T.-S. Jin, J.-S. Zhang, A.-Q. Wang, T.-S. Li, Synth. Commun. 34 (2004) 2611–2616;
(h) K. Friedrich, W. Ertel, Synthesis 2 (1970) 23;
(i) D.T. Mowr, J. Am. Chem. Soc. 67 (1945) 1050–1051.