European Journal of Medicinal Chemistry 138 (2017) 920–931

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Synthesis, molecular modeling studies and bronchodilation properties of nicotinonitrile containing-compounds

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ARTICLE INFO

Article history:
Received 24 April 2017
Received in revised form
30 June 2017
Accepted 16 July 2017
Available online 17 July 2017

Keywords:
Nicotinonitrile
Bronchodilation
QSAR
Pharmacophore

ABSTRACT

Facile synthetic pathway for nicotinonitriles **5a–o**, **7a–i** was demonstrated through reaction of ketones **4a–k**, **6a–f** with ylidenemalononitrile **3** in the presence of sodium alkoxide. Meanwhile, nucleophilic attack of amines on 2-bromonicotinonitrile **9** (obtained through reaction of propenone **8** with malononitrile, followed by bromination with bromine in acetic acid) afforded 3-pyridinecarbonitriles **11a–d**. Single crystal X-ray of compound **7i** reveals the monoclinic space group *C2/c* with 8 molecules per unit cell. Optimized structure of **7i** [DFT/B3LYP, 6-31G(d,p)] shows close correlations to that of X-ray study. Compound **5l** seems superior among all the synthesized analogues exhibiting bronchodilation properties about three folds potency compared to theophylline (standard reference) through pre-contracted tracheal rings with histamine standard method. Also compound **5a** reveals promising observations (about two folds potency of the standard reference). Molecular modeling studies (3D-pharmacophore and 2D-QSAR) supported the observed biological properties.

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1. Introduction

Nicotinonitrile is an important topic of heterocyclic systems due to the unique biological and pharmacological properties observed. 2-Amino-6-furan-2-yl nicotinonitriles were reported as A_{2A} adenosine receptor antagonists, which can implicated in chemotherapy of Parkinson's disease [1]. 2-Alkoxy-4-aminonicotinonitriles were documented as JNK inhibitors (c-Jun N-terminal kinase), serving as therapeutic modality in diseases with inflammatory symptoms such as asthma, stroke or Alzheimer's disease [2]. Wyeth research group published series of articles demonstrating the inhibitory properties of 3-pyridinecarbonitrile containing-compounds towards PKCθ, which is a member of protein kinase C (PKC) family belongs to serine/threonine kinases [3–11]. PKCθ inhibitors are associated with inflammatory disorders of many diseases such as, arthritis, asthma, sclerosis and colitis [12]. Milrinone **1** and Amrinone **2**, which are nicotinonitrile core, reported as phosphodiesterase-3 inhibitors used as cardiotonic agents (Fig. 1) [13–16].

The present study directs towards the synthesis and bronchodilation properties investigation of novel nicotinonitrile containing-compounds. Interest in the subject is supported by the fact that chronic obstructive pulmonary disease is the fourth leading cause of death globally and is predicted to occupy the third rank by 2030 according to WHO's reports [17]. Recently, we reported 4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles with halogenated phenyl as potential bronchodilators [18]. In the present study in continuation of our interest, we designed and synthesized a set of novel nicotinonitriles with 2,4-dichlorophenyl substitution. We have also studied molecular modeling including quantitative structure-activity relationship (QSAR) and 3D-pharmacophore to demonstrate the parameters responsible for the bio-properties and validate the biological observations.

2. Results and discussion

2.1. Chemistry

2-Alkoxy-4,6-diaryl nicotinonitriles **5a–o** were synthesized by the reaction of ylidenemalononitrile **3** [19] with acetophenones **4a–**

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http://dx.doi.org/10.1016/j.ejmech.2017.07.025
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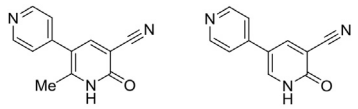


Fig. 1. Nicotinonitrile containing-compounds as phosphodiesterase-3 inhibitors.

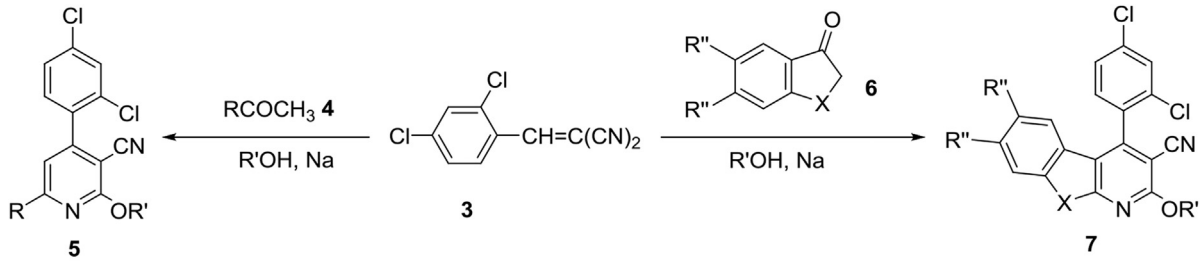
h or their related heterocyclic analogues **4i–k** in appropriate alcohol in the presence of sodium (Scheme 1). Spectroscopic (IR, ^{1}H- and ^{13}C-NMR) and elemental analysis data support the structures of **5a–o**. IR spectrum of **5a** (example of the synthesized family) shows the nitrile stretching vibration band ($\nu = 2222\ cm^{-1}$). The methoxy and pyridinyl *H*-5 are viewed at δ_H = 4.13, 7.32, respectively in ^{1}H-NMR spectrum of **5a**. ^{13}C-NMR spectrum of **5a** exhibits the pyridinyl *C*-3 and *C*-5 at δ_C = 95.0, 114.4, respectively. The methoxy and nitrile carbons are shown at δ_C = 54.8, 114.7, respectively.

The reaction is assumed to take place through addition of the acetophenone active methyl to the β-carbon of ylidene **3**. Alkoxide nucleophilic attack derived from the utilized alcohol at the nitrile group and cyclization due to dehydration and dehydrogenation gave the nicotinonitrile **5**. Cyclic ketones (1-indanone **6a**, 5,6-dimethoxy-1-indanone **6b**, α-tetralone **6c**, 1-benzosuberone **6d**, 4-chromanone **6e**, 4-thiochromanone **6f**) similarly react with ylidenemalononitrile **3** giving the nicotinonitrile containing-compounds **7a–i**. Single crystal X-ray studies of **7i** further support for the structure.

2-(Cyclic-amino)-4,6-diarylnicotinonitriles **11a–d** were obtained through nucleophilic attack of the secondary amines (piperidine **10a**, morpholine **10b**, 1-methylpiperazine **10c**, 1-ethylpiperazine **10d**) on 2-bromonicotinonitrile **9**. The latter was synthesized through Michael reaction of malononitrile with propenone **8** [20]. Then, bromination of the adduct formed with bromine in acetic acid (Scheme 2) (Supplementary Fig. S1–S87 show the spectral charts of the synthesized compounds **5a–o**, **7a–i**, **9** and **11a–c**).

2.2. Single crystal X-ray studies

Crystal structure of compound **7i** has been undertaken by single crystal X-ray diffraction. It contains a pyridinyl heterocycle connected to methoxy group at C19, nitrile group at C17 and dichlorophenyl ring at C10. The fused thiochromene ring is connected to the pyridinyl heterocycle through C1−C9 bond (Fig. 2). Compound **7i** is crystallized in a monoclinic space group *C2/c* with one



4a; R = Ph
4b; R = 2-Naphthyl
4c; R = 4-ClC_6H_4
4d; R = 4-FC_6H_4
4e; R = 4-BrC_6H_4
4f; R = 4-$H_3CC_6H_4$
4g; R = 4-$H_3COC_6H_4$
4h; R = 3,4-$(H_3CO)_2C_6H_3$
4i; R = 2-Thienyl
4j; R = 3-Pyridinyl
4k; R = 4-Pyridinyl

6a; X = CH_2, R'' = H
6b; X = CH_2, R'' = OCH_3
6c; X = $(CH_2)_2$, R'' = H
6d; X = $(CH_2)_3$, R'' = H
6e; X = OCH_2, R'' = H
6f; X = SCH_2, R'' = H

5a; R = Ph, R' = Me
5b; R = 2-Naphthyl, R' = Me
5c; R = 4-ClC_6H_4, R' = Me
5d; R = 4-ClC_6H_4, R' = Et
5e; R = 4-FC_6H_4, R' = Me
5f; R = 4-FC_6H_4, R' = Et
5g; R = 4-BrC_6H_4, R' = Me
5h; R = 4-BrC_6H_4, R' = Et
5i; R = 4-$H_3CC_6H_4$, R' = Me
5j; R = 4-$H_3COC_6H_4$, R' = Me
5k; R = 3,4-$(H_3CO)_2C_6H_3$, R' = Me
5l; R = 2-Thienyl, R' = Me
5m; R = 2-Thienyl, R' = Et
5n; R = 3-Pyridinyl, R' = Me
5o; R = 4-Pyridinyl, R' = Me

7a; R' = Me, R'' = H, X = CH_2
7b; R' = Et, R'' = H, X = CH_2
7c; R' = Me, R'' = OMe, X = CH_2
7d; R' = Me, R'' = H, X = $(CH_2)_2$
7e; R = Et, R'' = H, X = $(CH_2)_2$
7f; R = Me, R'' = H, X = $(CH_2)_3$
7g; R = Et, R'' = H, X = $(CH_2)_3$
7h; R = Me, R'' = H, X = OCH_2
7i; R = Me, R'' = H, X = SCH_2

Scheme 1. Synthetic route of 3-pyridinecarbonitrile containing compounds **5a–o** and **7a–i**.

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