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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design and synthesis of niflumic acid-based *N*-acylhydrazone derivatives as novel anti-inflammatory and analgesic agents

Amin Kheradmand · Latifeh Navidpour · Hamed Shafaroodi · Ghazaleh Saeedi-Motahar · Abbas Shafiee

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Abstract A new series of niflumic acid-based *N*-acylhydrazone derivatives **5a–p** were synthesized and evaluated for their anti-inflammatory and analgesic activities. Most of the compounds have shown anti-inflammatory activity with a moderate-to-excellent activity range (20–80 % reduction in inflammation). Among them, 3-chlorophenyl **5d** and 3-pyridyl derivatives **5o** exhibited the most potent anti-inflammatory activity relative to niflumic acid as the reference drug (77, 76, and 70 % reduction in inflammation at 1-h postdrug administration, respectively). Also, molecular simplification of niflumic acid through replacing the *N*-aryl group with *N*-methyl group produced compounds **6a–f** with anti-inflammatory activity in a quite similar manner to those of their parent derivatives. In this subgroup, 4-pyridyl derivative **6f** showed the most potent anti-inflammatory activity relative to niflumic acid (80 % reduction in inflammation at 1-h postdrug administration). The compounds with highest anti-inflammatory activity were subjected to analgesic assays and showed moderate-to-excellent analgesic activities. The compound **5j**, 4-methoxy derivative, exhibited the highest analgesic activity relative to niflumic acid (97 and 68 % activity, respectively).

A. Kheradmand · L. Navidpour (✉) · A. Shafiee (✉)
Department of Medicinal Chemistry, Faculty of Pharmacy and Drug Design & Development Research Center, Tehran University of Medical Sciences, 14176 Tehran, Iran
e-mail: navidpur@sina.tums.ac.ir

A. Shafiee
e-mail: ashafiee@ams.ac.ir

H. Shafaroodi · G. Saeedi-Motahar
Pharmacology and Toxicology Department, Pharmaceutical Sciences Branch and Pharmaceutical Sciences Research Center, Islamic Azad University, Tehran, Iran

Keywords Niflumic acid hydrazide · Anti-inflammatory · Analgesic

Introduction

The non-steroidal anti-inflammatory drugs (NSAIDs), which are also effective as analgesics, being widely prescribed medicines for treatment of pain, pyrexia, inflammation, and arthritis (Botting, 1999; Vane, 1971). These drugs block biosynthesis of prostaglandins (PGs) which are the important lipid mediators of inflammation as well as numerous homeostatic physiological functions by inhibiting enzyme PG H_2 endoperoxide synthase or cyclooxygenase (COX) enzymes. It is now well recognized; COX enzymes exist in two major isoforms, COX-1 and COX-2, which are responsible for cytoprotective effects and for inflammatory effects, respectively. COX-1 is known as a constitutive form of COX and expressed in all tissues, while COX-2 is an inducible form and expressed only in kidney, brain, and ovaries by pro-inflammatory molecules such as Interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), lipopolysaccharide (LPS), and tissue plasminogen activator (TPA) (Botting, 1999; Hawkey, 2000; Guslandi, 1997; Ziakas *et al*., 2005). It is found that housekeeping PGs produced by COX-1 are critical to the maintenance of normal renal function, gastric mucosal integrity, vascular hemostasis, and the autocrine response to circulating hormones. Classical NSAIDs may cause severe gastrointestinal (GI) toxicity such as bleeding, perforation, ulceration, and also cardiorenal complications due to indiscriminate inhibition of both COX isoforms which greatly limit their therapeutic usefulness (Yang *et al*., 2009; Girgis *et al*., 2007). Therefore, synthetic approaches based upon chemical modification of NSAIDs have been taken with the aim of improving their safety profile.

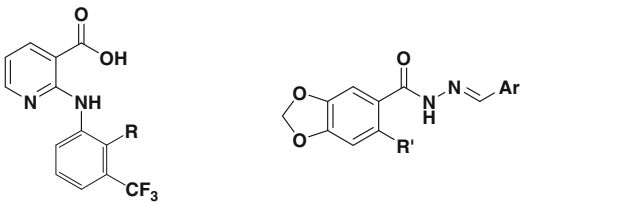


Fig. 1 Representative examples of pyridine derivatives of fenamates and *N*-acylarylhydrazones

Pyridine derivatives form an important class of heterocyclic compounds and have attracted the attention of many scientists (Sondhi *et al*., 2002; Effland and Klein, 1991). The pyridine nucleus is present in niflumic acid **1** and flunixin **2**, two traditional NSAIDs belonging to the class of fenamates (Fig. 1). Interestingly, the fenamates appears also to compete with PGs for binding at the PG receptor site in which this activity potentially antagonizes the physiopathological effects of PGs that have already been formed. However, fenamates are still endowed with most of the adverse effects induced by NSAIDs, particularly GI bleeding, ulceration, and perforation (Cocco *et al*., 2004).

Moreover, local irritation by the direct contact of the carboxylic acid (–COOH) moiety of NSAIDs with GI mucosal cells (topical effect) and decreased tissue PG production in tissues which undermine the physiological role of cytoprotective PGs in maintaining GI health and homeostasis (Smith *et al*., 1998; Hawkey *et al*., 2000) are two main factors that NSAIDs cause GI damage.

Some evidences suggest that the hydrazone moiety possesses a pharmacophoric character for the inhibition of COX in *N*-acylhydrazones (NAH) (Lima *et al*., 2000), due to their ability to mimic the bis-allylic moiety of unsaturated fatty acids, for example, arachidonic acid (AA), precursor of the eicosanoid biosynthesis (Fig. 1). Therefore, the derivatization of the carboxylic function with *N*-acylarylhydrazone having less acidic amide hydrogen has been taken with the aim of improving the safety profile.

Considering the above results and as a part of our ongoing program to design new anti-inflammatory agents (Almasirad *et al*., 2006; Moradi *et al*., 2010), herein, we describe the design, synthesis, and the biological evaluation of a novel diverse group of *N*-acylarylhydrazone derivatives of niflumic acid (**5**) and their simplified forms *N*-methyl analogs (**6**) with different substituents on the terminal phenyl (or pyridyl) ring.

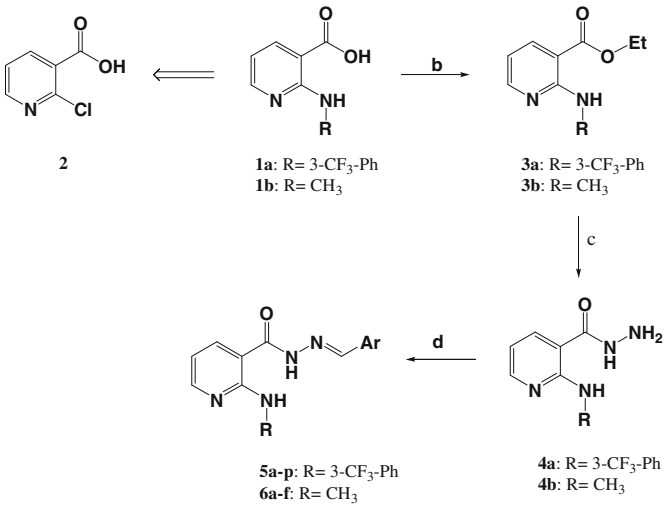
The most usual available method for the synthesis of substituted hydrazone in the literature is the acid catalyzed reaction of suitable hydrazine derivative with substituted aliphatic or aromatic aldehyde (Bezerra-Netto *et al*., 2006; Figueiredo *et al*., 2000; Duarte *et al*., 2007).

Results and discussion

Chemistry

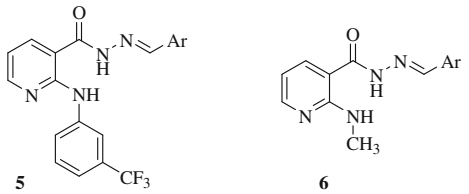
The synthetic reactions leading to the substituted arylidene-2-[(3-trifluoromethylanilino) or methylamino]nicotinic acid hydrazides (**5** and **6**) were outlined in Scheme 1.

2-Aryl (or alkyl) nicotinic acid hydrazides (**4a**–**b**) are key intermediates for the production of the title compounds **5a**–**p** and **6a**–**f**. The starting materials, 2-(3-trifluoromethylanilino)nicotinic acid (**1a**) was prepared by the reaction of 2-chloronicotinic acid **2** with 3-(trifluoromethyl)aniline in the presence of catalytic amount of potassium iodide (Hoffmann and Faure, 1968). Similarly, methylamino-dechlorination of compound **2** with aqueous solution of methylamine hydrochloride led to the formation of 2-(methylamino)nicotinic acid **1b**. Subsequently, acid-catalyzed esterification of latter compounds (**1a**–**b**) in ethanol



Scheme 1 Synthesis of niflumic acid-based NAH derivatives (**5** and **6**). *Reagents and conditions*: (*a*) $CH_3NH_2{\cdot}HCl$ or 3-CF_3-aniline, KI, 140 °C then 100 °C, 1.5 h; (*b*) EtOH, H^+; reflux, 16–18 h; (*c*) $NH_2NH_2{\cdot}H_2O$, EtOH, r.t. 24 h; (*d*) substituted aryl aldehydes, EtOH, HCl, r.t. 5–24 h

Table 1 2-Aryl (or alkyl)aminopyridine hydrazone derivatives **5** and **6**



5 **6**

Compound	Ar	AI acticity (%)[a]				
		at 30 min	at 1 h	at 2 h	at 3 h	at 4 h
5a	C_6H_5	60.35 ± 10.93	53.91 ± 7.47	36.75 ± 12.75	21.19 ± 10.67	30.98 ± 13.80
5b	3-FC_6H_4	58.25 ± 4.12	51.51 ± 6.35	52.76 ± 6.07	36.98 ± 3.90	29.75 ± 6.44
5c	4-FC_6H_4	33.87 ± 15.61	43.23 ± 13.96	41.16 ± 14.68	41.33 ± 14.73	36.53 ± 14.91
5d	3-ClC_6H_4	77.82 ± 2.18	76.70 ± 3.75	63.48 ± 4.71	55.21 ± 5.97	40.37 ± 8.78
5e	4-ClC_6H_4	52.38 ± 6.15	67.22 ± 3.48	52.75 ± 9.87	48.54 ± 9.47	43.71 ± 7.13
5f	3-OHC_6H_4	67.52 ± 9.03	63.80 ± 7.74	65.43 ± 8.31	48.99 ± 8.82	35.84 ± 7.24
5g	4-OHC_6H_4	59.25 ± 6.90	70.52 ± 7.92	68.01 ± 5.94	59.52 ± 9.95	61.61 ± 6.91
5h	3,4-$(OH)_2C_6H_3$	51.40 ± 5.82	50.80 ± 5.22	46.86 ± 6.12	38.24 ± 11.27	21.07 ± 9.78
5i	3-$OMeC_6H_4$	52.82 ± 3.15	58.75 ± 1.68	49.69 ± 4.17	30.26 ± 6.74	14.90 ± 6.65
5j	4-$OMeC_6H_4$	50.40 ± 6.87	59.42 ± 8.38	42.40 ± 3.56	26.46 ± 7.43	13.96 ± 5.43
5k	2,4-$(OMe)_2C_6H_3$	37.81 ± 8.18	55.69 ± 9.33	44.68 ± 9.33	24.11 ± 1.72	19.80 ± 6.54
5l	3,4-$(OMe)_2C_6H_3$	60.06 ± 4.91	70.02 ± 4.27	49.04 ± 7.84	44.01 ± 7.97	52.91 ± 7.55
5m	3,4,5-$(OMe)_3C_6H_2$	55.89 ± 6.34	54.36 ± 7.76	40.58 ± 10.15	28.52 ± 9.94	28.62 ± 8.87
5n	4-$Me_2NC_6H_4$	61.26 ± 5.75	63.47 ± 4.27	51.37 ± 3.24	39.49 ± 4.71	28.19 ± 3.03
5o	3-Pyridyl	59.08 ± 3.77	76.14 ± 4.13	62.36 ± 3.62	52.41 ± 4.07	36.03 ± 8.77
5p	4-Pyridyl	68.09 ± 3.35	70.16 ± 4.83	65.17 ± 8.03	54.93 ± 4.48	45.92 ± 5.26
6a	C_6H_5	56.46 ± 6.01	67.57 ± 5.18	47.19 ± 5.05	22.66 ± 5.95	14.78 ± 6.11
6b	3-ClC_6H_4	67.13 ± 4.74	68.62 ± 7.81	61.72 ± 2.56	39.55 ± 5.66	40.35 ± 4.27
6c	4-ClC_6H_4	46.46 ± 10.38	54.72 ± 9.42	54.13 ± 7.82	22.44 ± 7.64	18.19 ± 4.27
6d	3-$OMeC_6H_4$	56.12 ± 10.36	64.63 ± 8.60	51.46 ± 7.26	49.50 ± 11.88	42.25 ± 10.87
6e	3-Pyridyl	66.32 ± 6.39	61.14 ± 6.39	43.72 ± 7.73	27.69 ± 5.23	13.77 ± 5.22
6f	4-Pyridyl	63.20 ± 5.99	80.38 ± 1.91	60.44 ± 7.43	55.02 ± 8.0	15.46 ± 22.29
Niflumic acid		64.12 ± 6.88	70.41 ± 4.92	70.08 ± 10.06	70.58 ± 5.17	52.01 ± 7.12

[a] Inhibitory activity on carrageenan-induced rat paw edema. The results are expressed as mean ± SEM ($n = 4$–6) following a 10 mg/kg i.p. dose of the test compound

afforded corresponding ethyl esters **3** which on treatment with hydrazine hydrate gave related nicotinic acid hydrazides (**4a**–**b**) (Kamal *et al*., 2007).

Finally, with the hydrazide intermediate **4** in hands, the new NAH target compounds (**5a**–**p** and **6a**–**f**) were obtained in good to excellent yields, by condensing the hydrazide intermediate with the appropriate aldehydes in ethanol, using hydrochloric acid as catalyst (Table 1).

The next step of this work was to determine the relative configuration of the imine double bond of arylidenenicotinic acid derivatives **5**, **6**, to assure the diastereomeric ratio essential to the complete understanding of the biological effect. The careful analysis of the ^{1}H-NMR of **5** and **6** allowed us to detect the presence of one singlet signal related to the imine hydrogen at 8.2–8.55 ppm.

According to the literature, the hydrazone may exist as *Z*/*E* geometrical isomers about the C=N double bond or *cis*/*trans* amide conformers (Bezerra-Netto *et al*., 2006; Duarte *et al*., 2007; Figueiredo *et al*., 2000; Ribeiro *et al*., 1998).

To investigate the possible influence of the conformational restriction in the pharmacophoric NAH side chain, promoted by a possible intramolecular H-bond formation, molecular modeling studies using AM1 Hamiltonian were carried out in MOE 2008.10 program using the compounds **5a** and **6a** (Fig. 2). This study indicated that the compound bearing s-*trans* like conformation (conformation B, with 88 kcal/mol for **5a** and 70 kcal/mol for **6a**) has lower energy than the isomeric s-*cis* like conformation (conformation A, with 93–95 kcal/mol for **5a** and 76 kcal/mol for **6a**) (Fig. 2). In isomeric s-*trans* like conformation, the

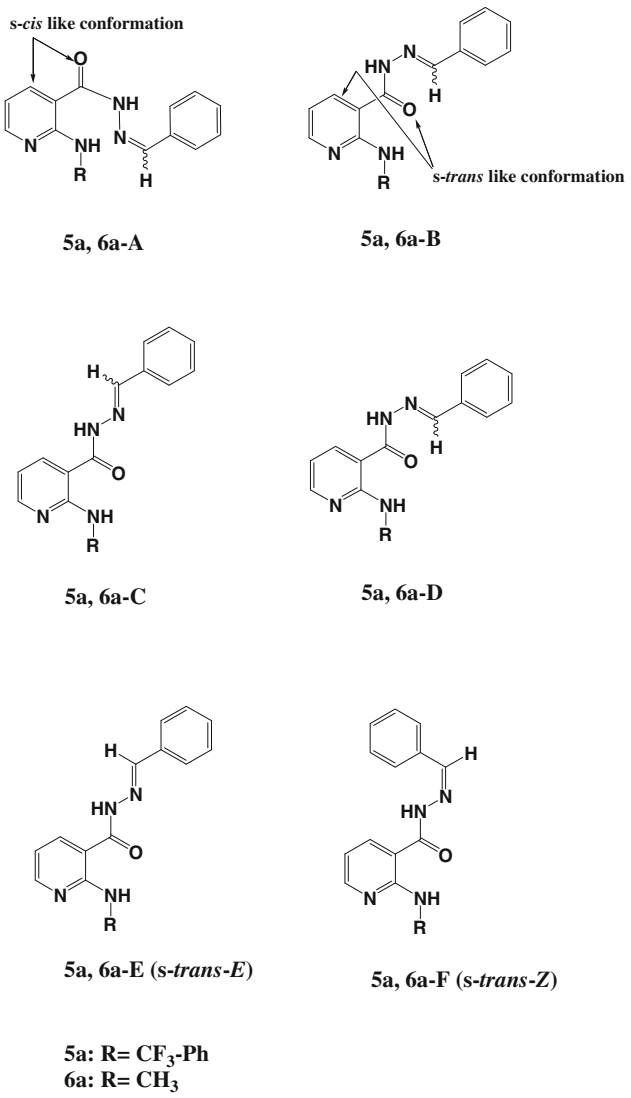


Fig. 2 Different possible conformations for **5a** and **6a**

possible intramolecular H-bond was formed between oxygen in C=O and NH of anilino substituent while in isomeric s-*cis* like conformation the hydrogen bonds was formed between N of anilino and NH of amidic group. Even though in both conformations A and B hydrogen bond formation is possible, but s-*trans* seems to be more stable.

Then, the systematic conformational analysis was carried out to determine which one of the conformers **C** or **D** (while the relative conformation of carbonyl and imino groups are different) is more stable. For derivative **5a**, the obtained value for the conformation **C** was 88 kcal/mol and for **6a** was 70 kcal/mol, while the energy found for the conformation **D** of **5a** was 92 kcal/mol and for **6a** was 75 kcal/mol (Fig. 2). Moreover, regarding the stereochemistry of hydrazone moiety, the (*E*)-diastereomer (**5a**: 90 kcal/mol and **6a**: 70 kcal/mol) was shown to be more stable than the corresponding (*Z*)-diastereomer (**5a**: 95 kcal/mol and **6a**: 75 kcal/mol). Therefore, conformation **E** was the most stable for **5a** and **6a** (Fig. 2).

Anti-inflammatory activity

In vivo pharmacological evaluation of **5a–p** and **6a–f** was carried out to assess their potential anti-inflammatory activity. Qualitative structure–activity relationship data acquired using the carrageenan-induced rat paw edema assay (Al-Haboubi and Zeitlin, 1983), showed that these group of compounds exhibit anti-inflammatory activity with a moderate-to-excellent activity range (20–77 % inhibition) in comparison with niflumic acid as the reference drug (52–70 % reduction in inflammation) at 30 min to 4 h (Table 1).

First, the substituents on the terminal phenyl moiety attached to the imine functional group of niflumic acid hydrazide derivatives **5** were rationally selected to acquire information about the influence of electronic and physicochemical parameters on pharmacological activity.

The analysis of the results revealed that introduction of small lipophilic chloro substituent (**5d**, **e**) or hydrophilic hydroxyl moiety (**5f**, **g**) produced compounds with improved anti-inflammatory activities (67–77 % reduction in inflammation at 1-h postdrug administration), while dimethylamino (**5n**) or methoxy (**5i**, **j**) substituted compounds were shown similar activities (58–63 % reduction in inflammation) for an i.p. dose of 10 mg/kg. Polysubstitution in most cases resulted in compounds with less activity.

Then, the effect of changing the position of substituents on the phenyl ring was investigated. In general, most of the meta substituted compounds (except for fluoro derivatives **5b**, **c**) were preferred over para substituted ones.

Substitution of phenyl moiety with pyridyl produced compounds with noticeably improved anti-inflammatory activity (70–76 % reduction in inflammation at 1-h postdrug administration).

Finally, among these analogs (**5a–p**), 3-chlorophenyl derivative (**5d**) showed the most potent anti-inflammatory activity relative to the niflumic acid as the reference drug (76 and 70 % reduction in inflammation at 1-h postdrug administration, respectively).

The effect of substitution of 3-trifluoromethylphenyl moiety with methyl group was next investigated. The analysis of results allowed us to suggest that most of the *N*–CH_3 analogs revealed respectable anti-inflammatory activities (54–80 %).

In the *N*–CH_3 series (**6a–f**), the compound having 4-pyridyl moiety attached to the imine functional group of nicotinic acid hydrazide derivative (**6f**) was the most active anti-inflammatory agent (80 % reduction in inflammation at 1-h postdrug administration).

Table 2 Analgesic activities of some of the **5** and **6** derivatives

Compound	R	Number of writhing[a]	Inhibition (%)
	CMC	48.75 ± 5.73	
5a	H	16.5 ± 2.3*	66.15*[b]
5d	3-ClC_6H_4	18.6 ± 5.9*	61.85*
5j	4-$OCH_3C_6H_4$	1.25 ± 0.75***	97.44***
5l	3,4-$(OMe)_2C_6H_3$	9.4 ± 2.3**	80.72**
5o	3-Pyridyl	23.7 ± 3.7*	51.38*
5p	4-Pyridyl	7.0 ± 1.9**	85.64**
6f	4-Pyridyl	4.6 ± 1.5***	90.56***
Niflumic acid		15.45 ± 6.9**	68.31**

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared to CMC group

[a] The compounds are administered at the dose of 10 mg/kg

[b] Analgesic activity relative to niflumic acid. *, ** and *** differed from control (CMC) group $P < 0.05$, $P < 0.01$ and $P < 0.001$, respectively

Analgesic activity

The compounds which exhibited significant anti-inflammatory activities comparable to that of the niflumic acid were subjected to analgesic assay.

The analgesic activities of the compounds were studied using acetic acid-induced abdominal constriction test (writhing test) (Whittle, 1964). Qualitative structure–activity relationship data, acquired using the analgesic assay, showed that most of the selected arylidene-2-(3-trifluoromethylanilino)nicotinic acid hydrazides were able to reduce the AcOH-induced constrictions with moderate-to-excellent activity range (51–97 % inhibition) in comparison with niflumic acid as the reference drug (68 % inhibition) (Table 2).

Interestingly, among substituted analog, 4-pyridyl (**5p** and **6f**) and 4-methoxyphenyl (**5j**) derivatives exhibited the most potent analgesic activity with 86, 91, and 97 % of inhibition, respectively, relative to the reference drug niflumic acid with 68 % of inhibition activity. This phenomenon can be explained by possible hydrogen bond formation between the nitrogen of 4-pyridyl or C-4 methoxy substituent on the phenyl ring with amino acids of target binding site.

Conclusion

Various substituted niflumic acid-based NAH derivatives were synthesized and screened for their potential anti-inflammatory activities. Most of the compounds have shown significant anti-inflammatory and analgesic activities. In carrageenan-induced rat paw edema assay, 3-chlorophenyl **5d** and 3-pyridyl derivatives **5o** exhibited the most potent anti-inflammatory activity. Then, a new series of NAH derivatives has been presented by molecular simplification of niflumic acid through replacing the *N*-aryl group with *N*-methyl group. Biological assay of these compounds exhibited a quiet similar manner to those of their parent derivatives. Selected compounds were subjected for writhing test and 4-methoxy derivative (**5j**) showed the most potent analgesic activity. Therefore, this new scaffold can be considered as a new lead for anti-inflammatory and analgesic agents.

Experimental protocols

Chemistry

Melting points were determined with a Reichert-Jung hot-stage microscope (Reichert-Jung, Germany) and are uncorrected. Infrared spectra were recorded on a Nicolet Magna 550-FT spectrometer (Nicolet, Madison, WI, USA). ^{1}H-NMR (400 MHz) spectra were measured on a Varian Unity plus 400 spectrometer (Zug, Switzerland) in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard, where *J* (coupling constant) values are estimated in Hertz. Elemental microanalyses were carried out with a Perkin-Elmer 240-C apparatus (Perkin-Elmer, Beaconsfield, UK) and were within ±0.4 % of the theoretical values for C, H, and N. All solvents and reagents were purchased from the Fluka, Aldrich (UK), or Merck Chemical Company (Germany). Male NMRI mice and male Wistar rats, used in the analgesic and anti-inflammatory screens, respectively, were purchased from Pasteur Institute (Karaj, Iran), and experiments were carried out using protocols approved by the ethics committee of Tehran University of Medical Sciences.

*2-(3-(Trifluoromethyl)anilino)nicotinic acid hydrazide (**4a**)*

To a solution of ethyl 2-(3-trifluoromethylanilino)nicotinate **3a** (1 mmol) in 10 ml of ethanol (5 mmol) 100 % hydrazine monohydrate was added. The reaction mixture was kept in room temperature for 24 h, and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was concentrated and the mixture was cooled. The precipitate obtained was filtered off, and recrystallized from ethanol affording the desired compound **4a** (70 %); m. p.: 146–148 °C.

IR (KBr): 3,308, 3,200 (NH), 1,635 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 11.05 (bs, 1H, NH, Ph-NH), 10.18 (bs, 1H, NH, hydrazide), 8.36 (dd, $J = 4.8$, 1.6 Hz, 1H, H_6, Pyr), 8.29 (s, 1H, H_2, Ph-NH), 8.06 (dd, $J = 7.6$, 1.6 Hz, 1H, H_4, Pyr), 7.78 (d, $J = 8.00$ Hz, 1H, H_4, Ph-NH), 7.52 (t, $J = 8.0$ Hz, 1H, H_5, Ph-NH), 7.28 (d, $J = 8.00$ Hz, 1H, H_6, Ph-NH), 6.91 (dd, $J = 7.6$, 4.8 Hz, 1H, H_5, Pyr), 4.65 (bs, 2H, NH, hydrazide).

^{13}C-NMR (DMSO-d_6): δ 166.98, 154.26, 150.71, 141.51, 136.94, 130.27, 130.0 (q, $J = 31.25$ Hz), 127.76 (q, $J = 271.25$), 123.10, 118.00, 115.24, 114.88, 111.51.

Anal. Calcd. for $C_{13}H_{11}F_3N_4O$: C, 52.71; H, 3.74; N, 18.91. Found: C, 52.88; H, 3.87; N, 18.82.

*2-(Methylamino)nicotinic acid hydrazide (**4b**)*

It was prepared according to procedure reported for **4a**.

Yield: 56 %; m. p.: 101–104 °C (ethanol).

IR (KBr): 3,395, 3,299, 3,219 (NH), 1,631 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 9.7 (bs, 1H, NH, hydrazide), 8.14 (d, $J = 4.4$ Hz, 1H, H_6, Pyr), 8.02 (bs, 1H, NH, methyl–NH), 7.79 (d, $J = 7.2$ Hz, 1H, H_4, Pyr), 6.52 (dd, $J = 7.2$, 4.4 Hz, 1H, H_5, Pyr), 4.14 (bs, 2H, NH, hydrazide), 2.89 (d, $J = 4.0$ Hz, 3H, CH_3).

^{13}C-NMR (DMSO-d_6): δ 167.78, 158.21, 151.33, 135.98, 110.67, 109.68, 28.05.

Anal. Calcd. for $C_7H_{10}N_4O$: C, 50.59; H, 6.07; N, 33.71. Found: C, 50.38; H, 6.22; N, 33.56.

General procedure for preparation of arylidene-2-(3-trifluoromethylanilino or methylamino) nicotinic acid hydrazides (**5** and **6**)

To a solution of 1 mmol of the hydrazide **4** in absolute ethanol (10 mL) containing one drop of 37 % hydrochloric acid 1.1 mmol of corresponding aromatic aldehyde derivative was added. The mixture was stirred at room temperature for 5–24 h, The progress of the reaction was monitored by TLC. After completion, the reaction mixture was neutralized with 10 % aqueous sodium carbonate solution, and the precipitate formed was filtered out and recrystallized from appropriated solvent.

*Benzylidene-2-(3-trifluromethylanilino)nicotinic acid hydrazide (**5a**)*

Yield: 80 %; m. p.: 182–184 °C (EtOAc/hexane).

IR (KBr): 3,298, 3,196 (NH), 1,639 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 12.10 (bs, 1H, NH, Ph-NH), 10.61 (bs, 1H, NH, hydrazide), 8.5–8.41 (*m*, 2H, H_6, Pyr & H, = CH-), 8.31 (s, 1H, H_2, Ph-NH), 8.22 (d, $J = 7.6$ Hz, 1H, H_4, Pyr), 7.87 (d, $J = 8.0$ Hz, 1H, H_4, Ph-NH), 7.82–7.74 (m, 2H, $H_{2,6}$, Ph), 7.58–7.45 (m, 4H, $H_{3,4,5}$, Ph & H_5, Ph-NH), 7.31 (d, $J = 8.0$ Hz, 1H, H_6, Ph-NH), 7.01 (dd, $J = 5.2$, 7.6 Hz, 1H, H_5, Pyr).

^{13}C-NMR (DMSO-d_6): δ 164.41, 154.57, 151.30, 149.15, 141.42, 138.00, 134.55, 130.82, 130.21, 129.93 (q, $J = 31.25$ Hz), 129.37, 127.69, 124.77 (q, $J = 271.25$ Hz), 123.47, 118.24, 115.70, 114.85, 111.87.

Anal. Calcd. for $C_{20}H_{15}F_3N_4O$: C, 62.50; H, 3.93; N, 14.58. Found: C, 62.58; H, 4.07; N, 14.42.

*(3-Fluorobenzylidene)-2-(3-trifluoromethylanilino) nicotinic acid hydrazide (**5b**)*

Yield: 85 %; m. p.: 196–198 °C (ethanol).

IR (KBr) : 3,332, 3,225 (NH), 1,644 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 12.21 (bs, 1H, NH, Ph-NH), 10.61 (bs, 1H, NH, hydrazide), 8.50–8.41 (m, 2H, H_6, Pyr & H, =CH–), 8.30 (*s*, 1H, H_2, Ph-NH), 8.22 (dd, $J = 7.6$, 1.6 Hz, 1H, H_4, Pyr), 7.89 (d, $J = 8.2$ Hz, 1H, H_4, Ph-NH), 7.68–7.50 (m, 4H, H_5, Ph-NH & $H_{2,4,6}$, Ph), 7.32–7.28 (m, 2H, H_6, Ph-NH & H_5, Ph), 7.01 (dd, $J = 7.6$, 4.8 Hz, 1H, H_5, Pyr).

^{13}C-NMR (DMSO-d_6): δ 164.58, 162.89 (d, $J = 242.5$ Hz), 154.63, 151.40, 147.73, 141.40, 138.26, 137.16 (*d*, $J = 7.5$ Hz), 131.47 (d, $J = 7.5$ Hz), 130.21, 129.92 (q, $J = 31.25$ Hz), 124.77 (q, $J = 270.0$ Hz), 124.08, 123.51, 118.26, 117.51 (d, $J = 21.25$ Hz), 115.74, 114.83, 113.50 (d, $J = 22.5$ Hz), 111.57.

Anal. Calcd. for $C_{20}H_{14}F_4N_4O$: C, 59.70; H, 3.51; N, 13.93. Found: C, 59.58; H, 3.37; N, 14.09.

*(4-Fluorobenzylidene)-2-(3-trifluoromethylanilino) nicotinic acid hydrazide (**5c**)*

Yield: 92 %; m. p.: 235–237 °C (ethanol).

IR (KBr): 3,347, 3,253 (NH), 1,645 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 12.11 (bs, 1H, NH, Ph-NH), 10.60 (bs, 1H, NH, hydrazide), 8.50–8.41 (m, 2H, H_6, Pyr & H, =CH–), 8.31 (s, 1H, H_2, Ph-NH), 8.21 (d, $J = 7.5$ Hz, 1H, H_4, pyr), 7.86 (d, $J = 7.5$, 1H, H_4, Ph-NH), 7.85–7.95 (dd, $J = 5.8$, 8.0 Hz, 2H, $H_{3,5}$, Ph), 7.52 (t, $J = 7.5$ Hz, 1H, H_5, Ph-NH), 7.37–7.27 (m, 3H, H_6, Ph-NH & $H_{2,6}$, Ph), 7.01 (dd, $J = 7.5$, 4.5 Hz, 1H, H_5, Pyr).

^{13}C-NMR (DMSO-d_6): δ 164.41, 163.73 (d, $J = 246.25$ Hz),154.56, 151.31, 147.98, 141.41, 137.99, 131.17, 130.20, 129.95 (q, $J = 31.25$ Hz), 129.88 (d, $J = 7.5$ Hz), 124.77 (q, $J = 270.0$ Hz), 123.47, 118.24, 116.45 (d, $J = 21.25$ Hz), 115.70, 114.84, 111.82.

Anal. Calcd. for $C_{20}H_{14}F_4N_4O$: C, 59.70; H, 3.51; N, 13.93. Found: C, 59.58; H, 3.27; N, 13.82.

*(3-Chlorobenzylidene)-2-(3-trifluoromethylanilino) nicotinic acid hydrazide (**5d**)*

Yield: 87 %; m. p.: 202–204 °C (ethanol).

IR (KBr): 3,328, 3,183 (NH), 1,641 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 12.28 (bs, 1H, NH, Ph-NH), 10.61 (bs, 1H, NH, hydrazide), 8.48–8.40 (m, 2H, H_6, Pyr & H, =CH–), 8.30 (s, 1H, H_2, Ph-NH), 8.25 (d, $J = 8.00$ Hz, 1H, H_4, Pyr), 7.88 (d, $J = 8.8$ Hz, 1H, H_4, Ph-NH), 7.82 (s, 1H, H_2, Ph), 7.72 (d, $J = 7.5$ Hz, 1H, H_6, Ph), 7.58–7.44 (m, 3H, H_5, Ph-NH & $H_{4,5}$, Ph), 7.31 (d, $J = 8.0$, 1H, H_6, Ph-NH), 7.01 (dd, $J = 8.0$, 4.8 Hz, 1H, H_5, Pyr).

^{13}C-NMR (DMSO-d_6): δ 164.50, 154.53, 151.19, 147.36, 141.29, 138.27, 136.82, 134.17, 131.23, 130.37, 130.21, 130.22 (q, $J = 32.5$ Hz), 126.85, 126.36, 124.73 (q, $J = 270.0$ Hz), 123.62, 118.37, 115.90, 114.78, 111.69.

Anal. Calcd. for $C_{20}H_{14}ClF_3N_4O$: C, 57.36; H, 3.37; N, 13.38. Found: C, 57.58; H, 3.21; N, 13.22.

*(4-Chlorobenzylidene)-2-(3-trifluoromethylanilino) nicotinic acid hydrazide (**5e**)*

Yield: 83 %; m. p.: 241–243 °C (ethanol).

IR (KBr): 3,344, 3,204 (NH), 1,637 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 12.20 (bs, 1H, NH, Ph-NH), 10.65 (bs, 1H, NH, hydrazide), 8.48–8.41 (m, 2H, H_6, Pyr & H, =CH–), 8.31 (s, 1H, H_2, Ph-NH), 8.21 (d, $J = 7.6$ Hz, 1H, H_4, pyr), 7.87 (d, $J = 8.0$ Hz, 1H, H_4, Ph-NH), 7.79 (d, 2H, $J = 7.6$ Hz, $H_{2,6}$, Ph), 7.61–7.46 (m, 3H, H_5, Ph-NH & $H_{3,5}$, Ph), 7.30 (d, $J = 8.0$ Hz, 1H, H_6, Ph-NH), 7.00 (dd, $J = 7.6$, 5.2 Hz, 1H, H_5, Pyr).

^{13}C-NMR (DMSO-d_6): δ 164.47, 154.60, 151.35, 147.75, 141.40, 138.00, 135.26, 133.50, 130.15, 129.82 (q, $J = 31.25$ Hz), 129.43, 129.27, 124.76 (q, $J = 270.0$ Hz), 123.46, 118.23, 115.74, 114.79, 111.71.

Anal. Calcd. for $C_{20}H_{14}ClF_3N_4O$: C, 57.36; H, 3.37; N, 13.38. Found: C, 57.20; H, 3.52; N, 13.22.

*(3-Hydroxybenzylidene)-2-(3-trifluoromethylanilino) nicotinic acid hydrazide (**5f**)*

Yield: 63 %; m. p.: 231–233 °C (ethanol).

IR (KBr): 3,437 (OH), 3,308, 3,202 (NH), 1,643 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 12.05 (bs, 1H, NH, Ph-NH), 10.64 (bs, 1H, NH, hydrazide), 9.68 (bs, 1H, OH, Ph), 8.42 (d, $J = 4.8$ Hz, 1H, H_6, Pyr), 8.36 (s, 1H, =CH–), 8.32 (s, 1H, H_2, Ph-NH), 8.21 (d, $J = 7.6$ Hz, 1H, H_4, pyr), 7.87 (*d*, $J = 7.6$ Hz, 1H, H_4, Ph-NH), 7.53 (*t*, 1H, $J = 7.6$ Hz, H_5, Ph-NH), 7.34–7.25 (m, 2H, H_6, Ph-NH & H_5, Ph), 7.23 (s, 1H, H_2, Ph), 7.14 (d, $J = 7.2$ Hz, 1H, H_6, Ph), 7.00 (dd, $J = 7.6$, 4.8 Hz, 1H, H_5, Pyr), 6.86 (d, $J = 7.6$ Hz, 1H, H_4, Ph).

^{13}C-NMR (DMSO-d_6): δ 164.35, 158.18, 154.54, 151.27, 149.28, 141.41, 138.00, 135.80, 130.42, 130.22, 129.93 (q, $J = 30.0$ Hz), 124.87 (q, $J = 270.0$ Hz), 123.49, 119.40, 118.19, 115.70, 114.86, 113.25, 111.91.

Anal. Calcd. for $C_{20}H_{15}F_3N_4O_2$: C, 60.00; H, 3.78; N, 13.99. Found: C, 59.78; H, 3.87; N, 13.82.

*(4-Hydroxybenzylidene)-2-(3-trifluoromethylanilino) nicotinic acid hydrazide (**5g**)*

Yield: 59 %; m. p.: 150–153 °C (ethanol).

IR (KBr): 3,440, 3,187, 3,149 (OH, NH), 1,664 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 12.05 (bs, 1H, NH, Ph-NH), 10.75 (bs, 1H, NH, hydrazide), 9.59 (bs, 1H, OH, Ph), 8.42–8.37 (m, 2H, H_6, Pyr & H, =CH–), 8.36–8.25 (m, 2H, H_2, Ph-NH & H_4, Pyr), 7.86 (d, $J = 8.0$ Hz, 1H, H_4, Ph-NH), 7.58 (d, $J = 8.0$ Hz, 2H, $H_{2,6}$, Ph), 7.54 (t, 1H, $J = 8.0$ Hz, H_5, Ph-NH), 7.32 (d, $J = 8.0$ Hz, 1H, H_6, Ph-NH), 7.00 (dd, $J = 7.6$, 5.2 Hz, 1H, H_5, Pyr), 6.87 (d, $J = 8.00$ Hz, 2H, $H_{3,5}$, Ph).

^{13}C-NMR (DMSO-d_6): δ 163.75, 160.25, 154.11, 149.75, 149.73, 140.89, 138.80, 130.38, 130.07 (q, $J = 31.25$ Hz), 129.46, 125.45, 124.70 (q, $J = 271.25$ Hz), 124.15, 118.89, 116.45, 116.28, 114.74, 112.57.

Anal. Calcd. for $C_{20}H_{15}F_3N_4O_2$: C, 60.00; H, 3.78; N, 13.99. Found: C, 60.12; H, 3.57; N, 14.15.

*(3,4-Dihydroxybenzylidene)-2-(3-trifluoromethylanilino) nicotinic acid hydrazide (**5h**)*

Yield: 61 %; m. p.: 157–159 °C (ethanol).

IR (KBr): 3,150–3,460 (OH, NH), 1,661 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ (ppm) 11.81 (bs, 1H, NH, Ph-NH), 10.70 (bs, 1H, NH, hydrazide), 9.40 (bs, 2H, OH, Ph), 8.40 (d, $J = 4.4$ Hz, 1H, H_6, Pyr), 8.32 (s, 1H, =CH–), 8.24 (s, 1H, H_2, Ph-NH), 8.18 (d, $J = 7.6$ Hz, 1H, H_4, Pyr), 7.85 (d, $J = 7.6$ Hz, 1H, H_4, Ph-NH),7.52 (t, $J = 7.6$ Hz, H_5, Ph-NH), 7.28 (d, 1H, $J = 7.6$ Hz, H_6, Ph-NH), 7.25 (s, 1H, H_2, Ph), 6.99 (dd, $J = 7.6$, 4.4 Hz, 1H, H_5, Pyr), 6.97 (d, $J = 8.0$ Hz, 1H, H_6, Ph), 6.79 (d, $J = 8.0$ Hz, 1H, H_5, Ph).

^{13}C-NMR (DMSO-d_6): δ 163.82, 154.27, 150.29, 149.92, 148.76, 146.24, 141.13, 138.43, 130.33, 130.01 (q, $J = 31.25$ Hz), 125.94, 124.74 (q, $J = 270.0$ Hz), 123.87, 121.21, 118.61, 116.13, 114.79, 113.41, 112.41.

Anal. Calcd. for $C_{20}H_{15}F_3N_4O_3$: C, 57.69; H, 3.63; N, 13.46. Found: C, 57.50; H, 3.85; N, 13.33.

*(3-Methoxybenzylidene)-2-(3-trifluromethylanilino) nicotinic acid hydrazide (**5i**)*

Yield: 67 %; m. p.: 183–186 °C (ethanol).

IR (KBr): 3,349, 3,207 (NH), 1,677 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 12.30 (bs, 1H, NH, Ph-NH), 10.70 (bs, 1H, NH, hydrazide), 8.48 (s, 1H, =CH–), 8.41 (d, $J = 4.4$ Hz, 1H, H_6, Pyr), 8.34–8.27 (m, 2H, H_4, Pyr & H_2, Ph-NH), 7.89 (d, $J = 7.2$ Hz, 1H, H_4, Ph-NH), 7.53 (t, $J = 7.2$ Hz, 1H, H_5, Ph-NH), 7.39 (t, $J = 8.0$ Hz, 1H, H_5, Ph), 7.34–7.27 (m, 3H, H_6, Ph-NH & $H_{2,6}$, Ph), 7.65–6.98 (m, 2H, H_5, Pyr & H_4, Ph-NH), 4.54 (s, 3H, OCH_3).

^{13}C-NMR (DMSO-d_6): δ 164.25, 160.03, 154.34, 150.62, 149.09, 141.12, 138.61, 136.01, 130.49, 130.30, 129.99 (q, $J = 30.0$ Hz), 124.74 (q, $J = 272.5$ Hz), 123.89,

120.71, 118.63, 117.03, 116.17, 114.80, 112.09, 111.57, 55.65.

Anal. Calcd. for $C_{21}H_{17}F_3N_4O_2$: C, 60.87; H, 4.14; N, 13.52. Found: C, 60.72; H, 3.97; N, 13.69.

*(4-Methoxybenzylidene)-2-(3-trifluromethylanilino) nicotinic acid hydrazide (**5j**)*

Yield: 73 %, m. p.: 210–213 °C (ethanol).

IR (KBr): 3,364, 3,271 (NH), 1,645 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 11.98 (bs, 1H, NH, Ph-NH), 10.66 (bs, 1H, NH, hydrazide), 8.41 (d, $J = 4.8$ Hz, 1H, H_6, Pyr), 8.38 (s, 1H, =CH–), 8.31 (s, 1H, H_2, Ph-NH), 8.20 (d, $J = 6.4$ Hz, 1H, H_4, Pyr), 7.87 (d, $J = 8.0$ Hz, 1H, H_4, Ph-NH), 7.70 (d, $J = 8.4$ Hz, 2H, $H_{2,6}$, Ph), 7.52 (t, $J = 8.0$ Hz, 1H, H_5, Ph-NH), 7.29 (d, $J = 8.0$ Hz, 1H, H_6, Ph-NH), 7.10–6.93 (m, 3H, $H_{3,5}$, Ph & H_5, Pyr), 3.82 (s, 3H, OCH_3).

^{13}C-NMR (DMSO-d_6): δ 164.19, 161.52, 154.56, 151.15, 149.07, 141.45, 137.89, 130.20, 130.01 (q, $J = 31.25$ Hz), 129.33, 127.09, 124.78 (q, $J = 270.0$ Hz), 123.40, 118.18, 115.64, 114.86, 111.96, 55.78.

Anal. Calcd. for $C_{21}H_{17}F_3N_4O_2$: C, 60.87; H, 4.14; N, 13.52. Found: C, 61.05; H, 4.01; N, 13.67.

*(2,4-Dimethoxybenzylidene)-2-(3-trifluromethylanilino) nicotinic acid hydrazide (**5k**)*

Yield: 57 %; m. p.: 181–184 °C (ethanol).

IR (KBr): 3,306, 3,208 (NH), 1,635 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 11.94 (bs, 1H, NH, Ph-NH), 10.74 (bs, 1H, NH, Pyr), 8.71 (s, 1H, =CH–), 8.40 (dd, $J = 4.8$, 1.6 Hz, 1H, H_6, Pyr), 8.31 (s, 1H, H_2, Ph-NH), 8.23 (dd, $J = 7.6$, 1.6 Hz, 1H, H_4, Pyr), 7.90–7.81 (m, 2H, H_4, Ph-NH & H_6, Ph), 7.53 (t, $J = 8.0$ Hz, 1H, H_5, Ph-NH), 7.30 (d, $J = 8.00$ Hz, 1H, H_6, Ph-NH), 6.99 (dd, $J = 7.6$, 4.8 Hz, 1H, H_5, Pyr), 6.70–6.61 (m, 2H, $H_{2,4}$, Ph), 3.87 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3).

^{13}C-NMR (DMSO-d_6): δ 164.08, 163.09, 159.76, 154.59, 150.97, 144.68, 141.50, 137.87, 130.22, 129.93 (q, $J = 31.25$ Hz), 127.15, 124.78 (q, $J = 270.0$ Hz), 123.30, 118.07, 115.50, 115.40, 114.79, 112.02, 106.94, 98.77, 56.25, 55.91.

Anal. Calcd. for $C_{22}H_{19}F_3N_4O_3$: C, 59.46; H, 4.31; N, 12.61. Found: C, 59.60; H, 4.47; N, 12.48.

*(3,4-Dimethoxybenzylidene)-2-(3-trifluromethylanilino) nicotinic acid hydrazide (**5l**)*

Yield: 71 %; m. p.: 197–199 °C (ethanol).

IR (KBr): 3,334, 3,230 (NH), 1,635 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 12.00 (bs, 1H, NH, Ph-NH), 10.70 (bs, 1H, NH, hydrazide), 8.41 (d, $J = 4.8$ 1H, H_6, Pyr), 8.36 (s, 1H, =CH–), 8.30 (s, 1H, H_2, Ph-NH), 8.20 (d, $J = 8.00$ Hz, 1H, H_4, Pyr), 7.88 (d, $J = 7.6$ Hz, 1H, H_4, Ph-NH), 7.52 (t, $J = 7.6$ Hz, 1H, H_5, Ph-NH), 7.37 (s, 1H, H_2, Ph), 7.29 (d, $J = 7.6$ Hz, 1H, H_6, Ph-NH), 7.22 (d, $J = 8.4$ Hz, 1H, H_6, Ph), 7.06–6.8 (*m*, 2H, H_5, Pyr & H_5, Ph), 3.83 (*s*, 3H, OCH_3), 3.82 (*s*, 3H, OCH_3).

^{13}C-NMR (DMSO-d_6): δ 164.17, 154.53, 151.45, 151.15, 149.58, 149.31, 141.45, 137.90, 130.21, 129.93 (q, $J = 31.25$ Hz), 127.22, 124.78 (q, $J = 270.0$ Hz), 123.40, 122.70, 118.18, 115.65, 114.83, 114.83, 112.02, 111.93, 108.57, 56.05, 55.91.

Anal. Calcd. for $C_{22}H_{19}F_3N_4O_3$: C, 59.46; H, 4.31; N, 12.61. Found: C, 59.23; H, 4.17; N, 12.70.

*(3,4,5-Trimethoxybenzylidene)-2-(3-trifluoromethylanilino) nicotinic acid hydrazide (**5 m**)*

Yield: 81 %; m. p.: 203–206 °C (ethanol).

IR (KBr): 3,371, 3,212 (NH), 1,640 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 10.40 (bs, 1H, NH, Ph-NH), 9.10 (bs, 1H, NH, hydrazide), 8.41 (d, $J = 4.8$ Hz, 1H, H_6, Pyr), 8.20–8.08 (m, 2H, H_2, Ph-NH & H, =CH–), 7.96–7.78 (m, 2H, H_4, Pyr & H_4, Ph-NH), 7.42 (t, 1H, $J = 8.0$ Hz, H_5, Ph-NH), 7.29 (d, $J = 7.6$ Hz, 1H, H_6, Ph-NH), 6.98 (s, 2H, $H_{2,6}$, Ph), 6.81 (dd, $J = 7.6$, 4.8 Hz, 1H, H_5, Pyr), 3.92 (s, 6H, OCH_3), 3.90 (s, 3H, OCH_3).

^{13}C-NMR (DMSO-d_6): δ 165.59, 154.70, 153.59, 150.08, 148.94, 141.95, 139.37, 138.33, 130.98, 130.17, 129.92 (q, $J = 31.25$ Hz), 124.85 (q, $J = 270.0$ Hz), 123.04, 117.64, 115.13, 114.71, 104.74, 60.55, 56.38.

Anal. Calcd. for $C_{23}H_{21}F_3N_4O_4$: C, 58.23; H, 4.46; N, 11.81. Found: C, 58.38; H, 4.27; N, 11.97.

*4-Dimethylaminobenzylidene-2-(3-trifluoromethylanilino) nicotinic acid hydrazide (**5n**)*

Yield: 81 %; m. p.: 225–226 °C (ethanol).

IR (KBr): 3,327, 3,207 (NH), 1,640 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 11.80 (bs, 1H, NH, Ph-NH), 10.75 (bs, 1H, NH, hydrazide), 8.40 (d, $J = 4.4$ Hz, 1H, H_6, Pyr), 8.32–8.25 (m, 2H, H_2, Ph-NH & H, =CH–), 8.18 (d, $J = 8.0$ Hz, 1H, H_4, Pyr), 7.86 (d, $J = 7.6$ Hz, 1H, H_4, Ph-NH), 7.56 (d, $J = 8.4$ Hz, 2H, $H_{2,6}$, Ph), 7.52 (t, $J = 7.6$ Hz, 1H, H_5, Ph-NH), 7.28 (*d*, $J = 7.6$ Hz, 1H, H_6, Ph-NH), 6.99 (dd, $J = 8.0$, 4.4 Hz, 1H, H_5, Pyr), 6.77 (d, $J = 8.4$ Hz, 2H, $H_{3,5}$, Ph), 2.99 (s, 6H, $-N(CH_3)_2$).

^{13}C-NMR (DMSO-d_6): δ 165.18, 154.71, 151.70, 149.84, 149.57, 142.14, 138.03, 130.19, 129.95, (q, $J = 31.25$ Hz), 128.95, 124.88 (q, $J = 270.0$ Hz), 122.82, 122.80, 117.39, 114.87, 114.67, 112.25, 40.30.

Anal. Calcd. for $C_{22}H_{20}F_3N_5O$: C, 61.82; H, 4.72; N, 16.39. Found: C, 61.68; H, 4.87; N, 16.22.

*(Pyridin-3-ylmethylene)-2-(3-trifluoromethylanilino) nicotinic acid hydrazide (**5o**)*

Yield: 87 %; m. p.: 195–197 °C (ethanol).

IR (KBr): 3,320, 3,215 (NH), 1,642 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 12.27 (bs, 1H, NH, Ph-NH), 10.58 (bs, 1H, NH, hydrazide), 8.90 (s, 1H, H_2, Pyr_2), 8.64 (d, $J = 4.4$ Hz, 1H, H_6, Pyr_2), 8.50 (s, 1H, 1-CH=), 8.44 (d, $J = 4.4$ Hz, H_6, Pyr_1), 8.31 (s, 1H, H_2, Ph-NH), 8.23 (d, $J = 7.6$ Hz, 1H, H_4, Pyr_1), 8.18 (d, $J = 7.6$ Hz, 1H, H_4, Pyr_2), 7.89 (d, $J = 8.0$ Hz, 1H, H_4, Ph-NH), 7.61–7.45 (m, 2H, H_5, Pyr_2 & H_5, Ph-NH), 7.31 (d, $J = 8.0$ Hz, 1H, H_6, Ph-NH), 7.03 (dd, $J = 7.6$, 4.4 Hz, 1H, H_5, Pyr_1).

^{13}C-NMR (DMSO-d_6): δ 164.55, 154.61, 151.40, 151.24, 149.22, 146.32, 141.36, 138.02, 134.07, 130.50, 130.11, 130.02 (q, $J = 31.25$ Hz), 124.75 (q, $J = 270.0$ Hz), 124.47, 123.47, 118.23, 115.77, 114.76, 111.53.

Anal. Calcd. for $C_{19}H_{14}F_3N_5O$: C, 59.22; H, 3.66; N, 18.17. Found: C, 59.38; H, 3.87; N, 18.02.

*(Pyridin-4-ylmethylene)-2-(3-trifluoromethylanilino) nicotinic acid hydrazide (**5p**)*

Yield: 83 %; m. p.: 245–248 °C (ethanol).

IR (KBr): 3,345, 3,257 (NH), 1,645 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 12.36 (bs, 1H, NH, Ph-NH), 10.53 (bs, 1H, NH, hydrazide), 8.60 (d, $J = 4.0$ Hz, 2H, $H_{2,6}$, Pyr_2), 8.45–8.38 (m, 2H, H_6, Pyr_1 & 1H, –CH=), 8.31 (s, 1H, H_2, Ph-NH), 8.23 (d, $J = 7.6$ Hz, 1H, H_4, Pyr_1), 7.88 (d, $J = 8.0$ Hz, 1H, H_4, Ph-NH), 7.71 (d, $J = 4.0$ Hz, 2H, $H_{3,5}$, Pyr_2), 7.53 (t, $J = 8.0$ Hz, 1H, H_5, Ph-NH), 7.32 (d, $J = 8.0$ Hz, 1H, H_6, Ph-NH), 7.03 (dd, $J = 7.6$, 4.4 Hz, 1H, H_5, Pyr_1).

^{13}C-NMR (DMSO-d_6): δ 165.99, 154.78, 150.63, 146.49, 142.44, 141.76, 138.61, 130.16, 129.81 (q, $J = 31.25$ Hz), 124.78 (q, $J = 270.0$ Hz), 123.26, 121.46, 117.86, 115.38, 114.75, 113.20.

Anal. Calcd. for $C_{19}H_{14}F_3N_5O$: C, 59.22; H, 3.66; N, 18.17. Found: C, 59.08; H, 3.47; N, 17.98.

*Benzylidene-2-(methylamino)nicotinic acid hydrazide (**6a**)*

Yield: 63 %; m. p.: 231–234 °C (butanol).

IR (KBr): 3,346, 3,272 (NH), 1,675 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 8.42 (s, 1H, –CH=), 8.21 (d, $J = 4.8$ Hz, 1H, H_6, Pyr), 8.04–7.98 (m, 2H, H_4, Pyr & H, $NHCH_3$), 7.70 (m, 2H, $H_{2,6}$, Ph), 7.49–7.41 (m, 3H, $H_{3,4,5}$, Ph), 6.6 (dd, $J = 7.6, 4.8$ Hz, 1H, H_5, Pyr), 2.92 (s, 3H, CH_3).

^{13}C-NMR (DMSO-d_6): δ 162.05, 153.26, 149.48, 141.96, 134.43, 130.91, 129.41, 127.68, 127.08, 115.32, 111.14, 29.71.

Anal. Calcd. for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.28; H, 5.37; N, 22.21.

*(3-Chlorobenzylidene)-2-(methylamino)nicotinic acid hydrazide (**6b**)*

Yield: 53 %; m. p.: 201–204 °C (butanol/EtOAc).

IR (KBr): 3,281, 3,185 (NH), 1,686 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 12.80 (bs, 1H, NH, hydrazide), 9.10 (bs, 1H, NH, –$NHCH_3$), 8.55 (s, 1H, –CH=), 8.51 (d, $J = 5.6$ Hz, H_6, Pyr), 8.15 (d, $J = 7.2$ Hz, 1H, H_4, Pyr), 7.79 (s, 1H, H_2, Ph), 7.70 (d, $J = 7.5$ Hz, 1H, H_6, Ph), 7.56–7.4 (m, 2H, $H_{4,5}$, Ph), 6.96 (dd, $J = 7.2$, 5.6 Hz, 1H, H_5, Pyr), 3.08 (s, 3H, CH_3).

^{13}C-NMR (DMSO-d_6): δ 162.16, 153.06, 148.22, 142.41, 136.70, 135.33, 134.17, 133.40, 131.33, 130.50, 129.40, 126.87, 126.37, 29.95.

Anal. Calcd. for $C_{14}H_{13}ClN_4O$: C, 58.24; H, 4.54; N, 19.40. Found: C, 58.36; H, 4.67; N, 19.54.

*(4-Chlorobenzylidene)-2-(methylamino)nicotinic acid hydrazide (**6c**)*

Yield: 72 %; m. p.: 221–223 °C (butanol/EtOAc).

IR (KBr): 3,350, 3,276 (NH), 1,674 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 12.53 (bs, 1H, NH, hydrazide), 8.99 (bs, 1H, NH, -$NHCH_3$), 8.51 (*s*, 1H, –CH=), 8.43 (d, $J = 5.2$ Hz, 1H, H_6, Pyr), 8.13 (d, $J = 7.2$ Hz, 1H, H_4, Pyr), 7.75 (d, $J = 7.5$ Hz, 2H, $H_{2,6}$, Ph), 7.53 (d, $J = 7.5$ Hz, 2H, $H_{3,5}$, Ph), 6.95 (dd, $J = 7.2$, 5.2 Hz, 1H, H_5, Pyr), 3.04 (s, 3H, CH_3).

^{13}C-NMR (DMSO-d_6): δ 161.96, 152.86, 148.27, 142.49, 140.95, 135.34, 133.39, 129.51, 129.30, 115.41, 111.17, 30.03.

Anal. Calcd. for $C_{14}H_{13}ClN_4O$: C, 58.24; H, 4.54; N, 19.40. Found: C, 58.38; H, 4.41; N, 19.22.

*(3-Methoxybenzylidene)-2-(methylamino)nicotinic acid hydrazide (**6d**)*

Yield: 47 %; m. p.: 175–177 °C (butanol).

IR (KBr): 3,412, 3,185 (NH), 1,630 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 11.90 (bs, 1H, NH, hydrazide), 8.36 (s, 1H, =CH–), 8.22 (d, $J = 4.8$ Hz, 1H, H_6, Pyr), 8.00–7.9 (m, 2H, H_4, Pyr & H, –$NHCH_3$), 7.37 (t, $J = 7.6$ Hz, 1H, H_5, Ph), 7.27 (m, 2H, $H_{2,6}$, Ph), 7.01 (d, $J = 7.6$ Hz, 1H, H_4, Ph), 6.61 (dd, $J = 7.2$, 4.8 Hz, 1H, H_5, Pyr), 3.80 (s, 3H, OCH_3), 2.90 (s, 3H, CH_3).

^{13}C-NMR (DMSO-d_6): δ 164.74, 160.00, 158.45, 151.98, 147.86, 137.01, 136.25, 130.43, 120.49, 116.66, 111.54, 110.63, 109.74, 55.61, 28.22.

Anal. Calcd. for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71. Found: C, 63.58; H, 5.80; N, 19.52.

*(Pyridin-3-ylmethylene)-2-(methylamino)nicotinic acid hydrazide (**6e**)*

Yield: 55 %; m. p.: 173–175 °C (ethanol).

IR (KBr): 3,483, 3,351 (NH), 1,639 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 12.00 (bs, 1H, NH, hydrazide), 8.85 (s, 1H, H_2, Pyr_2), 8.61 (d, $J = 4.4$ Hz, 1H, H_6, Pyr_2), 8.43 (s, 1H, =CH–), 8.24 (d, $J = 4.8$ Hz, 1H, H_6, Pyr_1), 8.12 (d, $J = 7.2$ Hz, 1H, H_4, Pyr_1), 7.98 (d, $J = 7.2$ Hz, 1H, H_4, Pyr_1), 7.49 (dd, $J = 4.4$, 7.2 Hz, 1H, H_5, Pyr_2), 6.63 (dd, $J = 4.8$, 7.2 Hz, 1H, H_5, Pyr_1), 2.92 (d, $J = 4.00$ Hz, 3H, CH_3).

^{13}C-NMR (DMSO-d_6): δ 164.13, 157.09, 150.79, 148.74, 145.42, 138.48, 134.37, 130.80, 129.44, 129.16, 124.68, 110.79, 28.65.

Anal. Calcd. for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43. Found: C, 61.38; H, 5.02; N, 27.60.

*(Pyridin-4-ylmethylene)-2-(methylamino)nicotinic acid hydrazide (**6f**)*

Yield: 71 %; m. p.: 274–277 °C (ethanol).

IR (KBr): 3,425, 3,281 (NH), 1,672 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 12.70 (bs, 1H, NH, hydrazide), 8.80 (m, 3H, $H_{2,6}$, Pyr_2 & H, NH, –$NHCH_3$), 8.50 (s, 1H, =CH–), 8.24 (d, $J = 4.8$ Hz, 2H, H_6, Pyr_1), 8.05–7.90 (m, 3H, H_4, Pyr_1 & $H_{3,5}$, Pyr_2), 6.82 (dd, $J = 4.8$, 7.2 Hz, 1H, H_5, Pyr_1), 2.99 (s, 3H, CH_3).

^{13}C-NMR (DMSO-d_6): δ 164.72, 158.76, 151.29, 147.93, 144.76, 136.28 129.27, 123.56, 111.02, 49.13.

Anal. Calcd. for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43. Found: C, 60.98; H, 5.29; N, 27.22.

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