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	Evento	379
	Actuación	519
	Oficio	
	Folios	2 1 1 7 7 8

Patente de Invención	☐	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (Fase Nacional)	☐	Capítulo I	☐ Capítulo II ☐
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Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

Solicitud de Suministro de Información

De acuerdo con el Art 46 D486, según el cual: "La Oficina Nacional competente podrá requerir el informe de expertos o de organismos científicos o tecnológicos que se consideren idóneos para que emitan opinión sobre la patentabilidad de la invención. Asimismo, cuando lo estime conveniente, podrá requerir informes de otras oficinas de propiedad industrial. De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederá de 3 meses, uno o más documentos relativos a una o más solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina: ...b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera... Si el solicitante no presentara los documentos requeridos dentro del plazo señalado en el presente artículo la oficina nacional competente denegará la patente"; y considerando que no ha sido posible para esta Oficina encontrar los documentos siguientes, atentamente se requiere su presentación:

MARZINZIK A L ET AL. "Key Intermediates in Combinatorial Chemistry: Access to Various Heterocycles from α , β -Unsaturated Ketones on the Solid Phase". *Journal of Organic Chemistry*. 1998, Vol 63, No 3, págs. 723-727.

Expediente 09 011 556 Art 46

BARTOLI G ET AL. "Reaction of dianions of acyclic .beta.-enamino ketones with electrophiles. 3. Nitriles: synthesis of pyridine and pyrimidine derivatives". *Journal of Organic Chemistry*., 1992, Vol 57, No. 22, 1995, págs. 6020 – 6025.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.

JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

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Revisó Jacqueline Alfonso.

OK. H

Synthesis of new 2-arylamino-6-trifluoromethylpyridine-3-carboxylic acid derivatives and investigation of their analgesic activity

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Abstract—A new series of 2-arylamino-6-trifluoromethyl-3-carboxylic acid derivatives was synthesized and assayed *in vivo* for their analgesic properties by means of writhing test in rats. When compared to aspirin, ibuprofen and flufenamic acid some of the new compounds exhibited a comparable or improved analgesic activity and a lower ulcerogenic effect.

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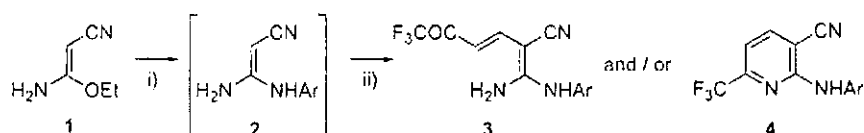
1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of compounds characterized by a similar pharmacological profile encompassing anti-inflammatory, analgesic and anti-pyretic activities. They are indicated for the treatment of musculo-skeletal disorders and other syndromes involving pain.¹ Despite their well-known therapeutic efficacy, NSAIDs have the potential to cause adverse reactions, especially with regard to the digestive and the renal system.² The most common adverse events related to the use of NSAIDs involve the gastrointestinal (GI) tract, and include a range of disorders, from functional problems such as dyspepsia, heartburn and abdominal discomfort to GI haemorrhage, peptic ulcer and perforation. Epidemiological studies have shown that approximately 10–20% of NSAID-treated patients have gastroduodenal erosions or ulcers detected at endoscopy, and 60% of those with serious GI complications are on long-term NSAID therapy.³ Given the vast epidemiological proportions of the problem of NSAID-induced GI damage, preclinical and clinical researchers have spent substantial efforts trying to identify the mechanisms responsible for the therapeutic and toxic effects of these drugs in order to devise strategies for effective prevention of GI toxicity.

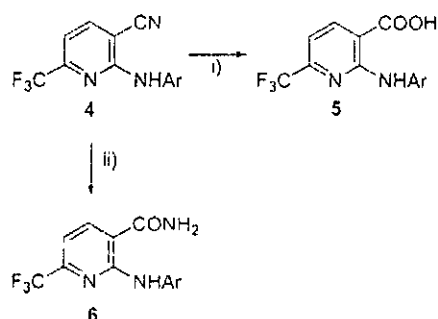
After Vane first established a link between NSAID pharmacological activity and prostaglandin production in 1971,⁴ subsequent studies have highlighted the central role of cyclo-oxygenase (COX) inhibition, with subsequent reduction of prostaglandin biosynthesis, in mediating both clinical efficacy and toxicity. In particular, NSAIDs inhibit the COX activity of prostaglandin G/H synthase, the enzyme that mediates the biotransformation of arachidonic acid into a series of prostanoids (prostaglandins and thromboxanes). These compounds display complex biological functions in several body systems and play a pivotal role in mediating inflammation and pain.^{5–7}

In the early 1990s, molecular biology studies identified two COX isoenzymes, named COX-1 and COX-2, which have different molecular structures and are encoded by different genes.⁸ Subsequent studies showed that COX-1 is constitutive and catalyses the production of prostaglandins involved in GI mucosal protection and other physiological activities, whereas COX-2, mostly inducible, is responsible for the production of prostaglandins that mediate inflammation, pain and fever.⁶ The discovery of these two different COX isoenzymes has allowed researchers a better understanding of the varying degrees of GI toxicity associated with the use of different NSAIDs by hypothesizing that COX-2 inhibition is responsible for the therapeutic effects of these drugs, whereas the typical adverse reactions are attributable to COX-1 inhibition.^{6,9} Recent

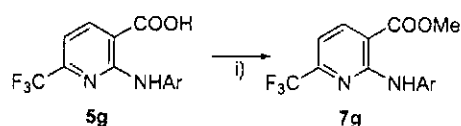
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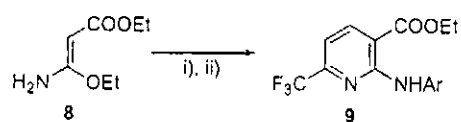
Scheme 1. Synthesis of pyridines 3. Reagents and conditions: (i) ArNH₂, MeCN, rt; (ii) 1,1,1-trifluoro-4-iso-butoxy-3-buten-2-one, 60 °C.



Scheme 2. Synthesis of pyridines 5 and 6. Reagents and conditions: (i) H₂SO₄, H₂O, 100 °C; (ii) 20% NaOH, 100 °C.



Scheme 3. Synthesis of pyridine 7g. Reagents and conditions: (i) DMF, DMA, Toluene, 90 °C.



Scheme 4. Synthesis of pyridines 8g-h. Reagents and conditions: (i) ArNH₂, MeCN, rt; (ii) 1,1,1-trifluoro-4-iso-butoxy-3-buten-2-one, 60 °C.

Cyanopyridines 4 were the starting materials for the preparation of pyridine-3-carboxylic acids 5 and pyridine-3-carboxamides 6 (Scheme 2). High yields of compounds 5 were achieved by hydrolysis of derivatives 4 in 50% aqueous sulfuric acid. Sodium hydroxide catalyzed hydrolysis of selected compounds 4 afforded pyridine-3-carboxamides 6.

Reaction of pyridine-3-carboxylic acid 5g with dimethylformamide dimethyl acetal (DMF–DMA), in toluene solution, afforded the corresponding methyl ester 7g in 80% yield. (Scheme 3).

A chemistry similar to that described in the synthesis of compounds 4 was used for the preparation ethyl esters 9.

As reported in Scheme 4, ethyl 3-amino-3-ethoxypropionate 8 was sequentially treated with the appropriate substituted arylamine, then with 1,1,1-trifluoro-4-iso-

butoxy-3-buten-2-one in MeCN solution to give pyridine derivatives 9.

2.2. Pharmacology

All compounds 4–7, 9 were screened for analgesic activity using acetic acid writhing test³⁵ in rats. Their activity as compared with three clinically used NSAIDs drugs namely aspirin (asa), ibuprofen (ibu) and flufenamic acid (flu) (Fig. 1).

The writhing test is a model of inflammatory pain that it has long been used as a screening tool for evaluation of putative analgesic and anti-inflammatory agents.^{36–38} Moreover this model has been shown to be useful in correlating the ED₅₀ values of NSAID antinociception in experimental animals with those in humans.^{39,40}

After ip administration all compounds 4 and 5, except for 4a, 4f and 5e, induced significant analgesic activity (at least $P < 0.05$ as compared to vehicle injected rats (Fig. 1). The percentage of inhibition of acetic acid-induced writhing (Table 1) revealed that all pyridine-3-carbonitriles 4, except for 4a and 4f, at the dose of 5 mg/kg displayed a similar analgesic activity induced by aspirin, ibuprofen and flufenamic acid (Fig. 1 and Table 1). Pyridine-3-carboxylic acids 5f, 5g and 5h induced a significantly higher analgesic activity as compared to the reference drugs ($P < 0.05$, Fig. 1). Acids 5a–5d show analgesic activity comparable to that of reference compounds (Fig. 1 and Table 1). Otherwise, administration of compounds 5e, 6, 7 and 9 did not induced a significant analgesic activity as compared to vehicle injected rats (Fig. 1 and Table 1).

In order to assess the possible nonspecific sedative or motor effects of the investigated compounds and to distinguish analgesia from drug-induced motor changes, the motor activity after ip administration of the most active compounds was evaluated (Fig. 2). None of the tested compounds 4 and 5 induced significant motor changes (Fig. 2) indicating that they give analgesia devoid of nonspecific sedative or stimulating effects.

Successively analgesic activity (Fig. 3) after po administration of the compounds that have shown analgesic activity after ip administration (4b, 4c, 4d, 4e, 4g, 4h, 5a, 5b, 5c, 5d, 5f, 5g, 5h) was evaluated. After po administration, compounds 4b–e, 4g, 4h, 5a–d and 5f–h at the dose of 10 mg/kg demonstrated noteworthy analgesic activity (at least $P < 0.05$ as compared to vehicle injected rats, Fig. 3) similar to that induced by the reference drugs.

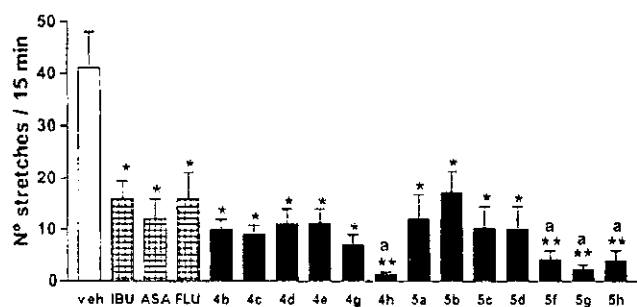


Figure 3. Stretches induced by ip acetic acid injection in rats pretreated po (60 min before) with vehicle, one of the reference drugs or one of the experimental new compounds (10 mg/kg). * $P < 0.05$, ** $P < 0.01$ as compared to vehicle pretreated rats; ^a $P < 0.05$ as compared to ibuprofen (ibu), aspirin (asa) and flufenamic acid (flu) pretreated rats.

to produce gastric ulcers compared to those induced by the three reference drugs. The severity of gastric damage was expressed as lesion index (Table 2).

Compounds **4b–e**, **4g**, **4h**, **5a–d** and **5f–h** at the dose of 100 mg/kg induced a significantly lower (compounds **4b**, **4c**, **4e**, **5b–d** and **5f–h**, lesion index between 0.1 and 0.7, Table 2) or no (compounds **4d**, **4h** and **5a**, lesion index: 0, Table 2) ulcerogenic effect as compared to reference drugs.

Analysis of all pharmacological data indicates that analgesic activity appears to be related to some structural requirements, to the presence of a 3-carboxylic acid moiety (compounds **5**) and to 2-arylamino substituents. In fact the amidation of the carboxyl on 3-position is detrimental for analgesic activity. As matter of fact if we consider the most active pyridine-3-carboxylic acid **5g** (percentage of inhibition of acetic acid-induced writhing 97%) the corresponding pyridine-3-carboxamide **6g** shows a 18% percentage of inhibition of acetic acid-induced writhing. The same trend is displayed by less ac-

tive compounds as **5e** (**5e**: 40%, **6e**: 31%). Similarly the esterification of 3-carboxylic function leads to the almost inactive compounds **7g** and **9g**. Independently from the kind of ester, methylic or ethylic, their values of percentage of inhibition of acetic acid-induced writhing are about the half of that showed by the parent acid **5g**. Generally substitution of 3-carboxylic group with a cyano moiety led to slight reduction in analgesic activity, except for compounds **5e** and **4e**, where this substitution have an helpful effect on the activity. The introduction of 2-methyl-5-chlorophenylamino or 2-methyl-6-chlorophenylamino functions at 2-position of showed by nitriles **4** and acids **5** is effective in inducing strong analgesic activity. The displacement of chlorine atom from 5- or 6-position to 4-position on the phenylamino ring produces variable effects: in nitriles (compound **4f**) is detrimental, while in acids the activity is maintained (compound **5f**). On the contrary displacement of chlorine atom from 5- or 6-position to 3-position does not affect activity in nitriles (compound **4e**), while it causes a drop in activity in acids (compound **5c**). When 2-methyl-6-chlorophenylamino group is replaced by a 2,6-dimethylphenylamino moiety as in **4d** and **5d** the activity is reduced.

3. Experimental

3.1. Chemistry

Melting points were determined on a Stuart Scientific Melling point SMP1 and are uncorrected. Proton NMR spectra were recorded on a Varian Unity 300 spectrometer. The chemical shift are reported in part per million (δ , ppm) downfield from tetramethylsilane (TMS), which was used as internal standard. Infrared spectra were obtained with a Bruker Vector 22 spectrophotometer. Elemental analyses were carried out with a Carlo Erba model 1106 Elemental Analyzer and the values found were within $\pm 0.4\%$ of theoretical values.

3.1.1. General procedure for the synthesis of 2-arylamino-6-trifluoromethylpyridin-3-carbonitriles 4. The appropriate arylamine (10 mmol) was added to a solution of 3-amino-3-ethoxypropenenitrile **1** (1.10 g, 10 mmol) in anhydrous acetonitrile (20 mL). The resulting solution was kept at room temperature for 4 days and then 1,1,1-trifluoro-4-*iso*-butoxy-3-buten-2-one (1.96 g, 10 mmol) was added. The resulting mixture was stirred at room temperature for 0.5 h and then refluxed for 6 h. Then solvent was removed to dryness. The resulting residue was triturated with isopropyl ether, the obtained solid was separated by filtration and recrystallized from a suitable solvent.

3.1.1.1. 2-((2-Methylphenyl)amino)-6-trifluoromethylpyridine-3-carbonitrile 4a. Yield 50%. Mp 138–140 °C (cyclohexane). ¹H NMR (CDCl₃): δ 2.34 (s, 3H, CH₃), 7.08–7.95 (m, 7H, aryl and NH). IR (Nujol) 3321, 2233.

Table 2. Gastric lesion index induced by an acute administration of the tested compounds (100 mg/kg po)

Compound	Ulcer index
ibu	37 $\pm$ 5.5
asa	58 $\pm$ 6.2
flu	4.83 $\pm$ 3
4b	0.5 $\pm$ 0.2 [*]
4c	0.33 $\pm$ 0.2 [*]
4d	0 [*]
4e	0.7 $\pm$ 0.2 [*]
4g	0.6 $\pm$ 0.2 [*]
4h	0 [*]
5a	0 [*]
5b	0.1 $\pm$ 0.1 [*]
5c	0.17 $\pm$ 0.1 [*]
5d	0.5 $\pm$ 0.2 [*]
5f	0.3 $\pm$ 0.15 [*]
5g	0.17 $\pm$ 0.1 [*]
5h	0.5 $\pm$ 0.1 [*]
vehicle	0 [*]

^{*} $P < 0.01$ as compared to ibuprofen (ibu), aspirin (asa) and flufenamic acid (flu).

for $C_{14}H_{10}ClF_3N_2O_2$: C, 50.85; H, 3.05; N, 8.47. Found: C, 50.80; H, 3.07; N, 8.44.

3.1.2.8. 2-((6-Chloro-2-methylphenyl)amino)-6-trifluoromethylpyridine-3-carboxylic acid 5h. Yield 92%. Mp 214–215 °C (toluene). ^1H NMR (DMSO- d_6): δ 2.26 (s, 3H, CH_3), 7.15–8.43 (m, 6H, aryl and NH), 10.38 (s, 1H, OH). IR (Nujol) 3384, 3338, 1668, 1618, 1580, 1541 cm^{-1} . Anal. Calcd for $C_{14}H_{10}ClF_3N_2O_2$: C, 50.85; H, 3.05; N, 8.47. Found: C, 50.79; H, 3.04; N, 8.51.

3.1.3. General procedure for the synthesis of 2-arylamino-6-trifluoromethylpyridine-3-carboxamides 6. The appropriate pyridine-3-carbonitrile **4** (10 mmol) was added of 20% aqueous sodium hydroxide solution (10 mL). The resulting mixture was heated in boiling water bath for 4 h. After cooling the reaction mixture was diluted with water (50 mL) and the formed precipitate was separated by filtration, dried and recrystallized from a suitable solvent.

3.1.3.1. 2-((3-Chloro-2-methylphenyl)amino)-6-trifluoromethylpyridine-3-carboxamide 6e. Yield 86%. Mp 234–235 °C (toluene). ^1H NMR (DMSO- d_6): δ 2.27 (s, 3H, CH_3), 7.11–8.44 (m, 7H, aryl and NH_2), 10.43 (s, 1H, NH). IR (Nujol) 3488, 3165, 3125, 1663, 1619, 1592 cm^{-1} . Anal. Calcd for $C_{14}H_{11}ClF_3N_3O$: C, 51.00; H, 3.36; N, 12.74. Found: C, 50.96; H, 3.37; N, 12.76.

3.1.3.2. 2-((5-Chloro-2-methylphenyl)amino)-6-trifluoromethylpyridine-3-carboxamide 6g. Yield 98%. Mp 214–215 °C (toluene). ^1H NMR ($CDCl_3$): δ 2.28 (s, 3H, CH_3), 6.98 (s, 2H, NH_2), 7.00–7.93 (m, 5H, aryl), 10.51 (s, 1H, NH). IR (Nujol) 3462, 3184, 1681, 1615 cm^{-1} . Anal. Calcd for $C_{14}H_{11}ClF_3N_3O$: C, 51.00; H, 3.36; N, 12.74. Found: C, 51.06; H, 3.35; N, 12.70.

3.1.3.3. Methyl 2-((5-chloro-2-methylphenyl)amino)-6-trifluoromethylpyridine-3-carboxylate 7g. To a solution of acid **5g** (0.83 g, 2.5 mmol) in dry toluene (5 mL), DMF–DMA (0.66 mL, 5 mmol) was added. The resulting solution was heated at 90 °C for 2 h. The solvent was removed at reduced pressure obtaining ester. Yield 80%. Mp 99–100 °C (cyclohexane). ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 7.01–8.37 (m, 5H, aryl), 10.14 (s, 1H, NH). IR (Nujol) 1693, 1617, 1590, 1542 cm^{-1} . Anal. Calcd for $C_{15}H_{12}ClF_3N_2O_2$: C, 52.26; H, 3.51; N, 8.13. Found: C, 52.31; H, 3.50; N, 8.14.

3.1.4. General procedure for the synthesis of ethyl 2-arylamino-6-trifluoromethylpyridine-3-carboxylates 9. The appropriate arylamine (10 mmol) was added to a solution of ethyl 3-amino-3-ethoxypropenoate **8** (1.60 g, 10 mmol) in anhydrous acetonitrile (20 mL). The resulting solution was kept at room temperature for 6 days and then 1,1,1-trifluoro-4-*iso*-butoxy-3-buten-2-one (1.96 g, 10 mmol) was added. The resulting mixture was stirred at room temperature for 0.5 h and then refluxed for 3 h. Then solvent was removed to dryness and the resulting residue was treated with isopropyl ether,

separated by filtration and recrystallized from a suitable solvent.

3.1.4.1. Ethyl 2-((5-chloro-2-methylphenyl)amino)-6-trifluoromethylpyridine-3-carboxylate 9g. Yield 80%. Mp 116–117 °C (hexane). ^1H NMR ($CDCl_3$): δ 1.44 (t, $J = 7.1$ Hz, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.43 (q, $J = 7.1$ Hz, 2H, CH_2), 7.04–8.42 (m, 5H, aryl), 10.23 (s, 1H, NH). IR (Nujol) 3278, 1696, 1619, 1600, 1590 cm^{-1} . Anal. Calcd for $C_{16}H_{14}ClF_3N_2O_2$: C, 53.57; H, 3.93; N, 7.81. Found: C, 53.62; H, 3.91; N, 7.77.

3.1.4.2. Ethyl 2-((6-chloro-2-methylphenyl)amino)-6-trifluoromethylpyridine-3-carboxylate 9h. Yield 80%. Mp 90–91 °C (hexane). ^1H NMR ($CDCl_3$): δ 1.44 (t, $J = 7.1$ Hz, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.43 (q, $J = 7.1$ Hz, 2H, CH_2), 7.04–8.42 (m, 5H, aryl), 10.23 (s, 1H, NH). IR (Nujol) 3318, 3262, 1693, 1616, 1601, 1587 cm^{-1} . Anal. Calcd for $C_{16}H_{14}ClF_3N_2O_2$: C, 53.57; H, 3.93; N, 7.81. Found: C, 53.52; H, 3.94; N, 7.84.

3.1.5. General procedure for the synthesis of 6-amino-5-cyano-6-arylamino-1,1,1-trifluoro-3,5-hexadien-2-ones 3. The appropriate arylamine (10 mmol) was added to a solution of 3-amino-3-ethoxypropenenitrile **1** (1.10 g, 10 mmol) in anhydrous acetonitrile (20 mL). The resulting solution was kept at room temperature for 4 days and then 1,1,1-trifluoro-4-*iso*-butoxy-3-buten-2-one (1.96 g, 10 mmol) was added. The resulting mixture was stirred at room temperature for 0.5 h and then refluxed for 3 h. Then solvent was removed to dryness. The resulting residue was constituted by a mixture of pyridine-3-carbonitriles **4** and 3,5-hexadienones **3**. These compounds were separated each other by treating the crude residue with EtOH. 3,5-hexadienones **3** precipitated and were separated by filtration; while pyridine-3-nitriles **4** were recovered from the ethanolic solution by removal of solvent.

3.1.5.1. 6-Amino-5-cyano-6-(3-trifluoromethylphenyl-amino)-1,1,1-trifluoro-3,5-hexadien-2-one 3b. Yield 40%. Mp 109–110 °C (cyclohexane). ^1H NMR ($CDCl_3$): δ 5.44 (s, 2H, NH_2), 7.05–8.09 (m, 6H, aryl, H-3 and H-4), 7.30 (s, 1H, NH). IR (Nujol) 3482, 3374, 3346, 2230, 1649, 1621, 1592 cm^{-1} . Anal. Calcd for $C_{14}H_9F_6N_3O$: C, 48.15; H, 2.60; N, 12.03. Found: C, 48.21; H, 2.59; N, 12.05.

3.1.5.2. 6-Amino-5-cyano-6-(4-trifluoromethylphenyl-amino)-1,1,1-trifluoro-3,5-hexadien-2-one 3c. Yield 32%. Mp 84–85 °C (cyclohexane). ^1H NMR ($CDCl_3$): δ 5.40 (s, 2H, NH_2), 5.74–7.71 (m, 6H, aryl, H-3 and H-4), 11.73 (s, 1H, NH). IR (Nujol) 3485, 3368, 2229, 1646, 1619, 1605, 1575 cm^{-1} . Anal. Calcd for $C_{14}H_9F_6N_3O$: C, 48.15; H, 2.60; N, 12.03. Found: C, 48.10; H, 2.61; N, 12.00.

3.1.5.3. 6-Amino-5-cyano-6-(3-chloro-2-methylphenyl-amino)-1,1,1-trifluoro-3,5-hexadien-2-one 3e. Yield 45%. Mp 114–115 °C (hexane). ^1H NMR ($CDCl_3$): δ

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