# *Synthesis and characterization of some ethoxyphthalimide substituted triazole derivatives assembled with pyridine and thiazolidinone heterocycles*

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*Síntesis y caracterización de derivados de triazol con un sustituyente etoxiftalimida unidos a heterociclos de piridina y tiazolidinona*

*Síntesi i caracterització de derivats de triazole amb substituent etoxiftalimida units a heterocicles de piridina i tiazolidinona*

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## RESUMEN

Se sintetizan nuevas 2-(fenil 4-sustituido)-3-{3-[(N-etoxiftalimido)sulfanil]-5-piridin-4-il-4H-1,2,4-triazol-4-il}-1,3-tiazolidin-4-onas (6a-d) mediante una secuencia de reacciones usando isoniazida (hidrazida del ácido isonicotínico) como producto de partida. Las estructuras de los compuestos sintetizados se asignan a partir del análisis elemental y de los datos espectroscópicos de IR y 1H RMN.

**Palabras clave:** Isoniazida, Araldehidos, Tiazolidinona, Bromuro de ftalimidoxietilo

## SUMMARY

Novel 2-(4-substitutedphenyl)-3-{3-[(*S*-*ethoxyphthalimido*) sulfanyl]-5-pyridin-4-yl-4*H*-1,2,4-triazol-4-yl}-1,3-thiazolidin-4-ones (6a-d) were synthesized *via* a multistep reaction sequence, using isoniazid (isonicotinic acid hydrazide) as starting material. The structures of the synthesized compounds were assigned on the basis of elemental analysis, IR and $^1$H NMR spectral data.

**Key Words:** Isoniazid, Araldehydes, Thiazolidinone, Phthalimidoxyethyl bromide

## RESUM

Es sintetitzen noves 2-(fenil 4-substituït)-3-{3-[(N-etoxiftalimido)sulfanil]-5-piridin-4-il-4H-1,2,4-triazol-4-il}-1,3-tiazolidin-4-ones (6a-d) mitjançant una seqüència de reaccions emprant isoniazida (hidrazida de l'àcid isonicotínic) com a producte de partida. Les estructures dels compostos sintetitzats s'assignen a partir de l'anàlisi elemental i de les dades espectroscòpiques de IR i 1H RMN.

**Mots clau:** Isoniazida, Araldehids, Tiazolidinona, Bromur de ftalimidoxietil

## INTRODUCTION

The 1,2,4-triazole system has widespread uses, and it has been considered as an interesting component in terms of biological activities such as anticonvulsant[1,2], antifungal[3-5], anticancer[6-8], antiinflammatory[9-11] and antibacterial properties[12-14]. Many triazole compounds have good fungicidal and plant growth regulating activities[15,16].

The chemistry of thiazolidin-4-one ring systems is of considerable interest as it is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities such as antidiarrheal[17], antimicrobial[18], antidiabetic[19], antihistaminic[20], anticancer[21], antiHIV[22], cardioprotective[23], anti-ischemic[24] and tumor necrosis factor-$\alpha$ antagonist activities[25].

Pyridine nucleus has been extensively explored for their versatile biological activities like anticancer and antitubercular etc[26,27]. Pyridine ring can be found in a broad variety of drugs, such as milirinone, which is useful for the treatment of the heart[28], alzheimer disease[29], anti-tumor[30] and anti amnesic agents[31]. A large number of imidoxy derivatives of various heterocycles reported to demonstrate a wide range of pharmacological activities like antimalarial[32], anticonvulsant[33], anticancer[34] etc. Several derivatives of this framework have been synthesized[35-38] by our reserch group.

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The pharmacological properties of 1,2,4-triazoles encouraged us to synthesize several new compounds featuring the above mentioned heterocyclic rings, attached to triazole moieties. As a part of our aim to search for biologically active heterocycles containing sulfur and nitrogen, we have synthesised a series of 2-(4-substitutedphenyl)-3-{3-[(*S-ethoxyphthalimido*) sulfanyl]-5-pyridin-4-yl-4*H*-1,2,4-triazol-4-yl}-1,3-thiazolidin-4-one **(6a-d)**.

## EXPERIMENTAL SECTION

**General Procedure**

Melting points were taken in open capillary tubes and are therefore uncorrected. Purity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using n-hexane and ethylacetate as solvent system. The visualization of spot was carried out in an iodine chamber. The IR spectra of the compounds were recorded in the 4000-450 $cm^{-1}$ ranges using KBr discs on FTIR IR RX1 Perkin Elmer spectrophotometers and $^1H$ NMR were recorded on a Bruker DRX-300 MHz spectrometer ($CDCl_3$) using TMS as an internal standard. The mass spectra were recorded on a Jeol SX-102 (FAB) mass spectrometer. Phthalimidoxyethyl bromide was prepared by reported methods[39].

Structure of all the synthesized compounds was assigned on basis of their analytical and spectral data.

**Synthesis of 5-pyridin-4-yl-1,3,4-oxadiazole-2(3*H*)-thione (1):**

A mixture of isoniazid (0.01mole) and KOH (0.015 mole) in ethanol was refluxed for 1 hr and dry carbondisulphide (0.015 mole) was slowly added to it. The reaction mixture was refluxed further for 8 hr on water bath. Excess of solvent was disttiled off and the residual mass poured into ice cold water. Then, the reaction content was acidified with conc. HCl. The precipitate was filtered off, washed with $H_2O$ and recrystallized from ethanol to get the desired compound.

**Synthesis of 4-amino-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (2):**

Hydrazine hydrate (0.04 mole) was added to a solution of (**1,** 0.01 mole) in ethanol and refluxed for 10 hr. Excess of ethanol and hydrazine hydrate were distilled under reduced pressure and the residual mass poured into ice cold water. The separated solid was washed with dilute acetic acid and recrystallized from ethanol.

**Synthesis of 4-[(4-substitutedphenylmethylidine) amino]-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (4a-d):**

An equimolar mixture of 4-amino-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **(2)** and 4-substitutedaraldehydes **(3a-d)** in ethanol was refluxed for 10 h with catalytic amount of glacial acetic acid. The progress of reaction was monitered by TLC. After reaction completion, the reaction mass was cooled to room temperature, and poured onto ice-cold water with vigorous string. The separated solid was filtered, washed with 5% sodium bisulfite solution to remove excess of aldehyde and recrystallized from ethanol.

**Synthesis of 2-(4-substitutedphenyl)-3-(3-pyridin-4-yl-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl)-1,3-thiazolidin-4-one (5a-d) :**

A solution of **(4a-d,** 0.01 mol) in DMF and mercaptoacetic acid (0.012 mol) was refluxed with a pinch of anhydrous $ZnCl_2$ for 10-14 hr on a water bath. After completion of reaction, excess of DMF was distilled off and the resulting product was treated with 5% NaHCO3 solution to remove unreacted mercaptoacetic acid. The separated product was washed with water, dried and recrystallized from DMF.

**Synthesis of 2-(4-substitutedphenyl)-3-{3-[(*S-ethoxyphthalimido*)sulfanyl]-5-pyridin-4-yl-4*H*-1,2,4-triazol-4-yl}-1,3-thiazolidin-4-one (6a-d):**

Compound (**5a-d**, 0.01mole) and phthalimidoxyethylbromide (0.01 mole) were dissolved in ethanol and refluxed for 12-14 hr with pyridine (3mL). Excess of solvent was removed under reduced pressure. On cooling, separated solid was recrystallized from ethanol.

## RESULTS AND DISCUSSION

In the present investigation, 5-pyridin-4-yl-1,3,4-oxadiazole-2(3*H*)-thione **(1)** was obtained on reacting isonicotinic acid hydrazide with $Br_2$ and ethanolic KOH. Formation of oxadiazole **(1)** was confirmed by the presence of C=N and N-H streching at 1595, 3310 $cm^{-1}$ in IR spectrum respectively. Compopund **(1)** undergo condensation with $N_2H_4.H_2O$ to form 4-amino-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **(2)**. Structure of compound **(2)** was elucidated on the basis of absence of C-O streching band in IR spectrum. Reaction of compound **(2)** with various araldehydes **(3a-d)** in presence of glacial acetic acid yielded corresponding arylidine derivatives **(4a-d)**. Presence of a singlet at $\delta$ 8.32 for Ar-CH confirms formation of **4b**. On cyclocondensation with mercaptoacetic acid compound **(4a-d)** was converted to their thiazolidinone derivatives **(5a-d)**. Formation of thiazolidinone ring was confirmed by the presence of a band at 1725 $cm^{-1}$ for C=O streching and a singlet at $\delta$ 4.6 for $CH_2$ protons in IR and NMR spectrum respectively. Subsequently, the SH proton was replaced by ethoxyphthlimide moiety to yield final compounds 2-(4-substitutedphenyl)-3-{3-[(*N*-ethoxyphthalimido) sulfanyl]-5-pyridin-4-yl-4*H*-1,2,4-triazol-4-yl}-1,3-thiazolidin-4-one **(6a-d).** Structure of which, was confirmed by presence of C=O and N-O stretching bands at 1755, 1723 and 1380 $cm^{-1}$ respectively in IR spectrum and new signals in $^1H$ NMR spectrum for side chain protons. The mass spectrum also supports the proposed structure by viewing molecular ion peaks of final compounds **(6a-d)**.


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The physical and analytical data are given in **Table 1** and spectral data are given in **Table 2**.

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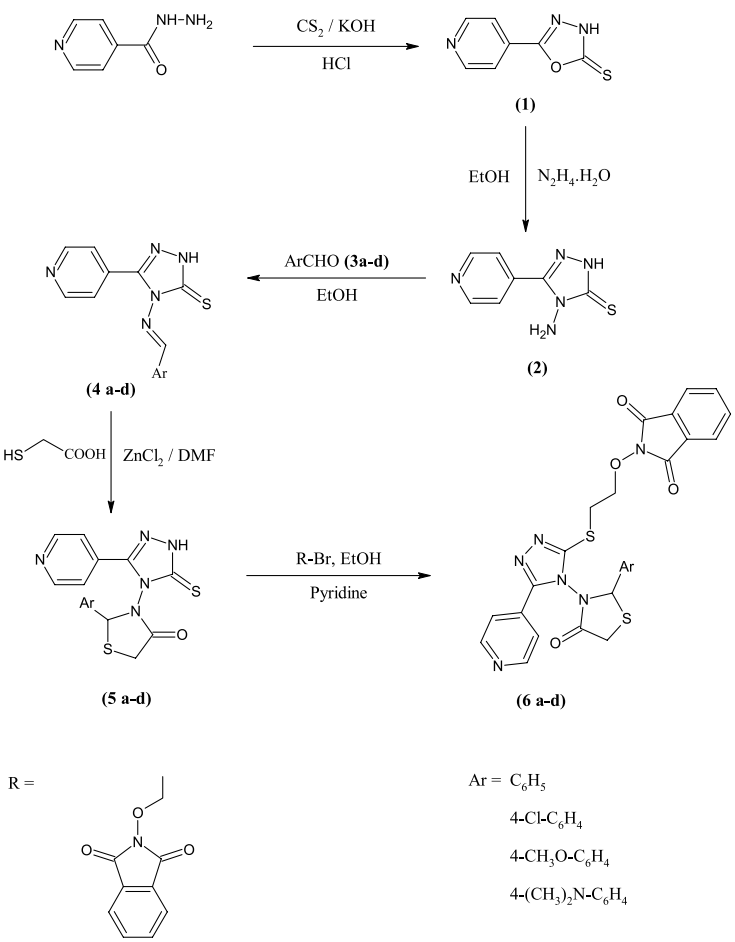


**Reaction Scheme**

*Table 1 : Characterization data of synthesized compounds*

| Compd. No. | Ar | Mol. Formula | Mol. weight | m.p. (°C) | Yield (%) | Calculated / Found (%) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N | S |
| 1 | – | $C_7H_5N_3OS$ | 179 | 204 | 88 | 46.92 (46.85) | 2.81 (2.77) | 23.45 (23.34) | 17.89 (17.80) |
| 2 | – | $C_7H_7N_5S$ | 193 | 249 | 81 | 43.51 (43.38) | 3.65 (3.62) | 36.24 (36.20) | 16.59 (16.46) |
| 4a | $C_6H_5$ | $C_{14}H_{11}N_5S$ | 281 | 184 | 85 | 59.77 (59.70) | 3.94 (3.97) | 24.89 (24.87) | 11.40 (11.32) |
| 4b | 4-Cl-$C_6H_4$ | $C_{14}H_{10}N_5SCl$ | 315 | 198 | 78 | 53.25 (53.19) | 3.19 (3.15) | 22.18 (22.10) | 10.15 (10.03) |
| 4c | 4-$CH_3O$-$C_6H_4$ | $C_{15}H_{13}N_5OS$ | 311 | 188 | 80 | 57.86 (57.78) | 4.21 (4.18) | 22.49 (22.36) | 10.30 (10.34) |
| 4d | 4-$(CH_3)_2N$-$C_6H_4$ | $C_{16}H_{16}N_6S$ | 324 | 210 | 62 | 59.24 (59.21) | 4.97 (4.88) | 25.91 (25.79) | 9.88 (9.79) |
| 5a | $C_6H_5$ | $C_{16}H_{13}N_5OS_2$ | 355 | 220 | 79 | 54.07 (54.02) | 3.69 (3.54) | 19.70 (19.66) | 18.04 (18.00) |
| 5b | 4-Cl-$C_6H_4$ | $C_{16}H_{12}N_5OS_2Cl$ | 389 | 224 | 66 | 49.29 (49.17) | 3.10 (2.95) | 17.96 (17.99) | 16.45 (16.33) |
| 5c | 4-$CH_3O$-$C_6H_4$ | $C_{17}H_{15}N_5O_2S_2$ | 385 | 200 | 60 | 52.97 (52.81) | 3.92 (3.90) | 18.17 (18.00) | 16.64 (16.50) |
| 5d | 4-$(CH_3)_2N$-$C_6H_4$ | $C_{18}H_{18}N_6OS_2$ | 398 | 232 | 70 | 54.25 (54.21) | 4.55 (4.48) | 21.09 (21.07) | 16.09 (15.97) |
| 6a | $C_6H_5$ | $C_{26}H_{20}N_6O_4S_2$ | 544 | 269 | 69 | 57.34 (57.38) | 3.70 (3.59) | 15.43 (15.26) | 11.78 (11.61) |
| 6b | 4-Cl-$C_6H_4$ | $C_{26}H_{19}N_6O_4S_2Cl$ | 578 | 280 | 56 | 53.93 (53.90) | 3.31 (3.18) | 14.51 (14.43) | 11.08 (10.94) |
| 6c | 4-$CH_3O$-$C_6H_4$ | $C_{27}H_{22}N_6O_5S_2$ | 574 | 245 | 59 | 56.43 (56.41) | 3.86 (3.84) | 14.63 (14.71) | 11.16 (11.00) |
| 6d | 4-$(CH_3)_2N$-$C_6H_4$ | $C_{28}H_{25}N_7O_4S_2$ | 587 | 180 | 52 | 57.23 (57.09) | 4.29 (4.22) | 16.68 (16.51) | 10.91 (10.81) |

*Table 2 : Spectral data of synthesized compounds 1- 6(a-d)*

| **Compd. No.** | **Spectral Data** | |
|---|---|---|
| 1 | IR ($cm^{-1}$): | 1595 (C=N str.), 3310 (N-H str.), 3037 (Ar-H str.) |
| | $^1$H NMR (δ): | 7.61-8.26 (m, 4H, Ar-H), 8.1 (s, 1H, NH) |
| 2 | IR ($cm^{-1}$): | 3326, 3260, 3100 (N-H str.) |
| | $^1$H NMR (δ): | 7.97 (s, 2H, $NH_2$) |
| 4a | IR ($cm^{-1}$): | 1610 (C=N str.), 3090 (N-H str.) |
| | $^1$H NMR (δ): | 8.20 (s, 1H, Ar-CH=) |
| 4b | IR ($cm^{-1}$): | 1663 (C=N str.), 3125 (N-H str.), 765 (C-Cl str.) |
| | $^1$H NMR (δ): | 8.32 (s, 1H, Ar-CH=) |
| 4c | IR ($cm^{-1}$): | 1600 (C=N str.), 3078 (N-H str.), 1122 (C-O str.) |
| | $^1$H NMR (δ): | 3.78(s, 3H, $OCH_3$), 8.18 (s, 1H, Ar-CH=) |
| 4d | IR ($cm^{-1}$): | 1585 (C=N str.), 3070 (N-H str.) |
| | $^1$H NMR (δ): | 3.29 (s, 6H, $NMe_2$), 8.15 (s, 1H, Ar-CH=) |
| 5a | IR ($cm^{-1}$): | 1770 (C=O str.), 710 (C-S-C str.) |
| | $^1$H NMR (δ): | 4.2 (s, 2H, $CH_2$), 3.3 (s, 1H, Ar-CH) |
| 5b | IR ($cm^{-1}$): | 1725 (C=O str.), 760 (C-S-C str.), 750 (C-Cl str.) |
| | $^1$H NMR (δ): | 4.6 (s, 2H, $CH_2$), 3.5 (s, 1H, Ar-CH) |
| 5c | IR ($cm^{-1}$): | 1680 (C=O str.), 683 (C-S-C str.) |
| | $^1$H NMR (δ): | 4.0 (s, 2H, $CH_2$), 3.1 (s, 1H, Ar-CH), 3.75 (s, 3H, $OCH_3$) |
| 5d | IR ($cm^{-1}$): | 1688 (C=O str.), 678 (C-S-C str.) |
| | $^1$H NMR (δ): | 3.96 (s, 2H, $CH_2$), 3.2 (s, 1H, Ar-CH), 2.98 (s, 6H, $NMe_2$) |
| 6a | IR ($cm^{-1}$): | 1389 (N-O str.), 1750, 1730 (C=O str.) |
| | $^1$H NMR (δ): | 4.17 (t, 2H, O-$CH_2$), 2.97 (t, 2H, S-$CH_2$) |
| 6b | IR ($cm^{-1}$): | 1429 (N-O str.), 1755, 1723 (C=O str.) |
| | $^1$H NMR (δ): | 4.26 (t, 2H, O-$CH_2$), 3.37 (t, 2H, S-$CH_2$) |
| 6c | IR ($cm^{-1}$): | 1372 (N-O str.), 1768, 1710 (C=O str.) |
| | $^1$H NMR (δ): | 4.09 (t, 2H, O-$CH_2$), 2.84 (t, 2H, S-$CH_2$) |
| 6d | IR ($cm^{-1}$): | 1360 (N-O str.), 1760, 1777 (C=O str.) |
| | $^1$H NMR (δ): | 4.13 (t, 2H, O-$CH_2$), 2.80 (t, 2H, S-$CH_2$) |