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1,2,4 - TRİAZOLİN - 3 - TİYONLARDAN ELDE EDİLEN BAZI TİYOÜRE TÜREVLERİNİN SENTEZ VE KARAKTERİZASYONLARI

SYNTHESIS AND CHARACTERIZATIONS OF SOME THIOUREA DERIVATIVES FROM 1,2,4 - TRIAZOLINE - 3 - THIONES

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SUMMARY

A number of N - substituted - N'- [4 - (4- methyl / phenyl - 2,4 - dihydro - 3H - 1,2,4 - triazole - 3 - thione - 5 - yl) phenyl] thiourea derivatives were obtained by the reactions of 5- (4- aminophenyl)-4- methyl- 2,4 - dihydro- 3H-1,2,4- triazole -3- thione with methyl, allyl, phenyl and p- bromophenyl isothiocyanates; and also by the reactions of 5- (4- aminophenyl) - 4- phenyl - 2,4 - dihydro-3H-1,2,4- triazole - 3 - thione with methyl, ethyl, allyl, cyclohegzyl, phenyl and p - chlorophenylisothiocyanates. The structures and purity of synthesised compounds were confirmed using UV, IR and MASS spectroscopic techniques. Compounds (V c, d, i, j) exhibited no molecular ion peaks in the mass spectra were also confirmed with elemental analysis.

ÖZET

Çeşitli N - sübstitüe - N' - [4 - (4 - metil / fenil- 2,4 - dihidro - 3H - 1,2,4 - triazol - 3 - tiyon - 5 - il) fenil] tiyoüre türevleri, 5- (4- aminofenil) - 4 - metil- 2,4 - dihidro - 3H - 1,2,4 -triazol- 3- tiyonun metil, allil, fenil ve p- bromofenil izotiyosiyanatlara, 5- (4-aminofenil)- 4 - fenil- 2,4 - dihidro- 3H - 1,2,4 - triazol - 3 - tiyonun da metil , etil, allil, siklohegzil, fenil ve p - klorofenil izotiyosiyanatlara katımıyla kazanıldı. Sentez edilen bileşiklerin yapıları ve saflıkları UV, IR ve MASS spektroskopik yöntemleri ile aydınlatıldı. Kütle spektrumunda moleküler iyon piki vermeyen bileşiklerin (Vc, d, i,j) yapıları ayrıca elementel analizle kanıtlandı.

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INTRODUCTION

Both thiourea and diphenylurea derivatives are known to exhibit significant tuberculostatic (1,2,3) and antiviral (4) activities respectively. Certain 1,2,4 - triazole derivatives have also the similar effects (5,6,7). In addition, antibacterial activities of thioureas (8,9) and 1,2,4 - triazoles (10, 11, 12); antifungal activities of 1,2,4- triazoles (13,14); and also hypoglycaemic activities of some 1,2,4- triazoles (15, 16, 17) and antihypertensive effects of 1,2,4 - triazolyl thiourea derivaties (18,19) have been reported. In a structure - activity relationship study, Galabov and his co - workers (4) showed that the aniviral activity of diphenylthiourea derivatives was due to the - NHC (=S) NH- function in the molecule and that the positive / negative changes in this activity depended on its substitutents. The compounds Va - j have the same pharmacophoric group. Morever, the fact that the compounds IVa and IVb had positive response against Candida albicans and Candida tropicalis (14) supports the possible antimicrobial activities of compounds Va - j. These all prompted us to combine the thiourea moiety with 1,2,4 - triazole structure to design more potent drugs. Therefore, we undertook the synthesis of N - substituted - N'- [4 - (4 – methyl / phenyl - 2,4 - dihydro - 3H-1,2,4 - triazole - 3 - thione - 5 - yl) phenyl] thiourea derivatives. We now report these ten 1,2,4 - triazole derivatives having different alkyl / aryl groups and the thiourea moiety in the structure (Figure 1).

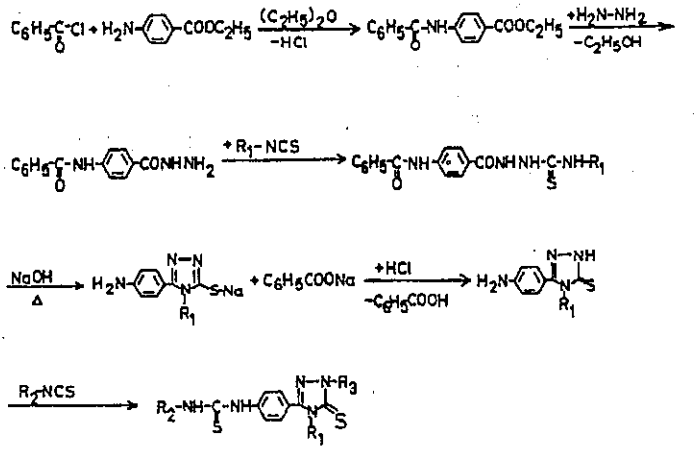


Figure – 1 : Synthetic route for N – alkyl – N' [(4 – methyl – 2,4 – dihydro – 3H – 1,2,4 – triazole – 3 – thione – 5 – yl) phenyl] thiourea derivatives.

MATERIALS AND METHODS

Materials and Instruments : The chemicals used in the experiments were purchased from Merck Company. All melting points were recorded on a Buchi 510 melting point apparatus and uncorrected. Laboratory solvents were predried using standard procedures. IR spectra were recorded on a Perkin - Elmer 240 spectrometer as KBr pellets. Mass spectra were obtained on KRATOS MS - 9 / 50 Double Focussing Mass Spectrometer. Elemental analysis was performed on a CEST MOD 110 Analyser. UV spectra were recorded on a Shimadzu UV 254 spectrometer (1mg / mL in ethanol).

Methods

Preparation of ethyl - p- (benzolyamino) benzoate (I) : To a solution of Benzocain (0.03 mol in diethylether), was added dropwise benzoyl chloride (0,03 mol in diethylether). The precipitate was filtered and washed with water. The product was recrystallised from ethanol (20).

Preparation of p- (benzoylamino) benzoic acid hydrazide (II) : A mixture of I (0.011 mol) and hydrazine hydrate (0.185 mol) was refluxed at 110 - 130°C for 45 min. To this mixture was added ethanol (10 mL) and was further refluxed for one hour. The precipitate was filtered and washed with water and ethanol (21) [Yield : 71 % ; m. p. : 235° C].

Synthesis of 1 - [p- (benzoylamino) benzoyl] - 4- alkyl / aryl thiosemicarbazides (III a - b) : II (0.0075 mol) in ethyl alcohol (90 mL) was heated for 15 min. To this mixture was added isothiocyanate (0.0075 mol) and further heated for 1.5 hours. The white precipitate was several times washed with ethanol (22). [Yield : 92.2 % ; m. p. : 239°C for 1- [p- (benzoylamino) benzoyl] - 4 - methylthiosemicarbazide (IIIa) and yield : 86 % ; m. p.: 260°C for 1- [p- (benzoylamino) benzoyl] - 4 - phenyl thiosemicarbazide (IIIb)]

Synthesis of 4,5 - disubstituted - 2,4 - dihydro- 3H - 1,2,4 - triazole - 3 - thiones (IV a- b) : A mixture of IIIa or IIIb (0.004 mol) and NaOH solution (12 mL, 2N) was refluxed for 4 hours. On cooling, it was solidified (sodium salt of IV a-b). This was dissolved in water and acidified with concentrated HCl. The precipitate was washed with water and was recrystallised from ethanol (14) [Yield: 89.8 %; m. p. : 180° C for 5- (4 - aminophenyl) - 4 - methyl - 2,4 -dihydro - 3H -1,2,4- triazole -

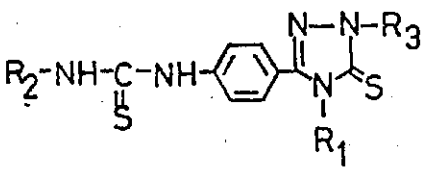
3- thione (IVa) and yield : 65.1% ; m. p. : 282 -288 °C for 5- (4-aminophenyl)- 4- phenyl - 2,4 - dihydro - 3H-1,2,4- triazole - 3- thione (IVb).

Synthesis of N - substituted - N' - [4 - (4- alkyl/ aryl - 2,4 - dihydro- 3H -1,2,4 - triazole -3- thione -5-yl) phenyl] thioureas (Va - j) : IVa or IVb (0.003 mol), methanol (10 mL) and dioxane (5 mL) were heated and added to isothiocyanate (0.003 mol). The reaction mixture was refluxed for 4 hours. The solvent was then evaporated and the crude product was recrystallised from ethanol.

RESULTS AND DISCUSSION

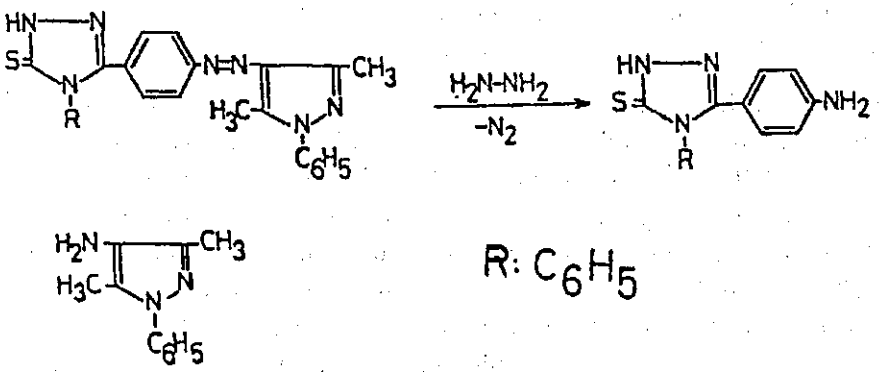
The present method yielded the desired N - Alkyl / aryl - N'- [4- (4-methyl/ phenyl-2,4 - dihydro- 3H -1,2,4 - triazole -3- thione-5-yl) phenyl] thiourea derivatives in a pure state according to the route presented in figure 1.

Table – 1 : General structure and substituents of N – alkyl / arly – N' – [(4 – methyl – 2,4 – dihydro – 3H – 1, 2, 4 – triazole – 3 – thione – 5 – yl) phenyl] thiourea derivatives

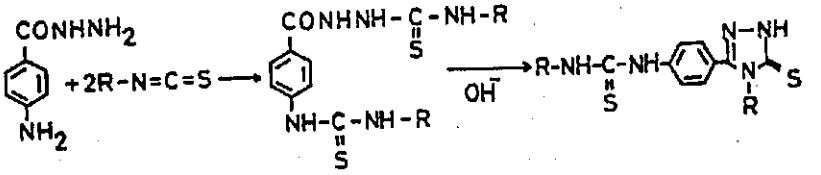


Compound	R_1	R_2	R_3
Va	$-CH_3$	$-CH_3$	H
Vb	$-CH_3$	$-CH_2-CH=CH_2$	H
Vc	$-CH_3$	$-C_6H_5$	H
Vd	$-CH_3$	$-C_6H_4$ Br (p.)	$-CSNHC_6H_4$ Br (p.)
Ve	$-C_6H_5$	$-CH_3$	H
Vf	$-C_6H_5$	$-C_2H_5$	H
Vg	$-C_6H_5$	$-CH_2-CH=CH_2$	H
Vh	$-C_6H_5$	$-C_6H_{11}$	H
Vi	$-C_6H_5$	$-C_6H_5$	H
Vj	$-C_6H_5$	$-C_6H_5$ Cl (p.)	H

In the synthesis of 1,2,4 - triazoline -3- thiones, basic cyclization procedures has been employed ie heating 1- acyl-4- alkyl / arylthiosemicarbazides in alkaline (14, 23, 24, 25). In the present work this method was also carried out. In addition, following benzoylation of benzocaine, protection of amino group was achieved during the following two reactions. Free amino function (IV a-b) was re - gained by the effect of heating and alkaline used in the cyclization of III a-b to give IVa-b. Thus, compounds carrying different substitutents at the fourth position of triazole ring and the terminal nitrogen of thiourea (Va-j) became possible to be synthesized. The compound IVb was previously synthesized by Rollas with the reductive cleavage of the azo compound with excess of hydrazine hydrate (20, 26). Since this method required a multistep reaction, the more economic former method was employed.



In order to synthesize substituted thiourea derivatives, the amine compounds have been reported to be reacted with a variety of isothiocyanates in various solvents such as ethanol, benzene, DMF, acetone, o - dichlorobenzene, pyridine : water (1:1) and dioxane (1,2,3,8,9,18,19,23,27). In the present study, dioxane: methanol (1:2) was tried and proved useful. Of Va - j series, all compounds, except compound Vi, reported in the present work were original. However, Vi was previously prepared with a different procedure (23,28). In these studies, a number of thiosemicarbazides were obtained by reacting p - aminobenzoicacid hydrazide with various isothiocyanates. Basic cyclizations of these thiosemicarbazides were then carried out to give Vi.



The melting points, yield, elemental analysis, UV and IR spectra, and mass fragments of compounds (Va - j) are given in table 2.

The maximum absorption at 253 - 259 nm is a characteristic of 1,2,4 - triazoline - 3 - thiones (29, 30). There is also a batochromic shift as a third absorption maxima because of increased aromaticity. IR spectra of compounds Va-j showed that the characteristic absorption bands of thiolactam C=S, aromatic C=C and triazoline C=N are in line with the literature values (9, 14, 20, 24, 26) (table 2). The thiourea C=S (1310 - 1340 cm^{-1}); thiourea and 1,2,4- triazoline -3- thione N -H (3200 - 3360 cm-1) absorption bands are also consistent with the literature (9,31). In addition, the presence of absorption bands between 1180 and 1195 cm^{-1} and the lack of an absorption band at 2600 cm^{-1} due to SH function verifies the thione form of 1,2,4- triazoline structures. Of the compounds Va - j, the ones which have aromatic ring in R_2 position did not give the molecular ion peaks in mass analysis (Table 2). In those cases, the elemental analysis confirmed the structure. However, all the compounds showed similar fragmentation patterns as observed previously for either thioureas or 1, 2, 4 – triazoline – 3 – thiones (32) such as losing the pertinent R_2NH_2 or R_2NCS from the molecular ion. More detailed Mass findings will be described elsewhere. The pharmacological activity of compounds Va-j are currently under investigation.

^1H - NMR of compound Vf : DMSO - d6 /TMS , (ppm) 1.1 (s, 3H, CH_3); 3.42 - 3.45 (q, 2H, CH_2); 7.18 - 7.64 (m, 9H, Ar - H); 7.84(s, 1H, thiourea N - H); 9.48 (s, 1H, thiourea N' - H); 13.98 (s, 1H, triazoline N - H) (figure 2).

Table – 2 : Analytical and spectral data for N – alkyl / aryl – N' – [(4 – methyl – 2, 4 – dihydro – 3H – 1, 2, 4 – triazole – 3 – thione – 5 – yl)

Compound	Molecular Formula (M.Wt.)	Mass (m/e)	m.p. (°C)	Yield (%)	Elemental Analysis (Calc./Found.) C	H	N	UV (EtOH) max.(nm)	IR (KBr) (cm⁻¹) C=S**	C=S***
V_a	$C_{11}H_{13}N_5S_2$ (279.377)	279(M^+)	211–213	98.20	–	–	–	201.1 253.6 295	1330	1180
V_b	$C_{12}H_{15}N_5S_2$ (305.415)	305(M^+)	172–175	92.14		–	–	201 254.9 297	1330–1310	1190
V_c	$C_{16}H_{15}N_5S_2$ (341.448)	308(M^+–33)	162–165	39.83	56.28 56.54	4.43 4.59	20.51 19.62	202.5 258.4 290.2	1340	1180
V_d	$C_{23}H_{18}Br_2N_6S_3$ (634.45)	401(M_+–233)	120–124	37.85	43.53 43.51	2.84 3.67	13.24 12.46	201.3 283.3	1330	1195
V_e	$C_{16}H_{15}N_5S_2$ (341.448)	341(M^+)	249–251	67.69	–	–	–	201.3 257 302.6	1330	1180
V_f	$C_{17}H_{17}N_5S_2$ (355.475)	355(M^+)	254	61.69	–	–	–	200.2 258 302.3	1330	1180
V_g	$C_{18}H_{17}N_5S_2$ (367.486)	367(M^+)	223	82.28	–	–	–	200.4 257 305.0	1325–1310	1190
V_h	$C_{21}H_{23}N_5S_2$ (409.566)	409(M^+)	277–280	41.45	–	–	–	203.4 259.4 301.8	1330	1180
V_i	$C_{21}H_{17}N_5S_2$ (403.512)	369(M^+–34)	205	86.19	62.53 61.45	4.21 4.30	17.33 16.38	200.9 260* 309.8	1320	1180
V_j	$C_{21}H_{16}ClN_5S_2$ (437.964)	324(M^+–114)	225	59.63	57.59 57.58	3.68 4.07	15.99 16.40	202.0 261* 315.9	1320	1180

* shoulder ; ** thiourea ; *** 1, 2, 4 – triazole – 3 – thione

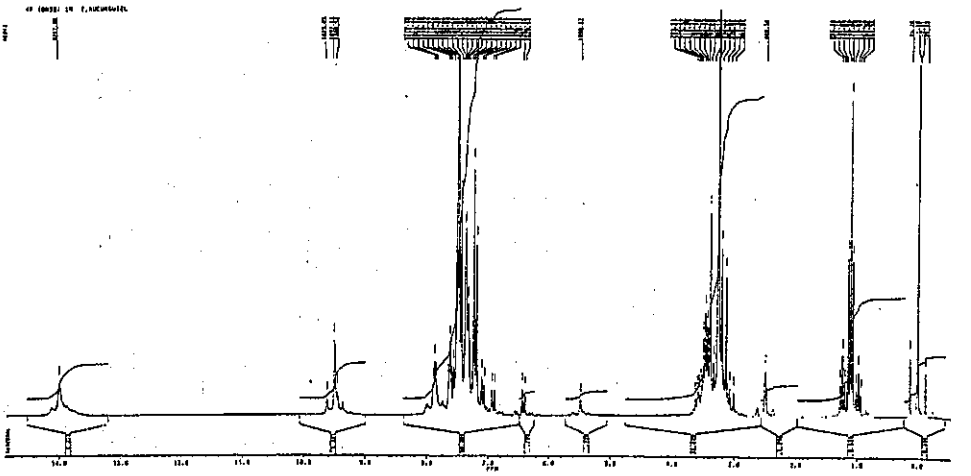


Figure – 2 : ^{1}H – NMR Spectrum of Compound Vf.

REFERENCES

1. Buu - Hoi, Xuong, D., Nam, H. : *J. Chem. Soc.*, 1573 (1955).
2. Doub, L., Richardson, L. M., Herbst, D. R., Black, M. L., Stevenson, O. L., Bombas, L. L., Youmans, G. P., Youmans, A. S. : *J. Chem. Soc.*, **80**, 2205 (1958).
3. Glasser, A. C., Doughty, R. M. : *J. Pharm. Sci.*, **51**, 1031 (1962).
4. Galabov, A. S., Galabov, B. S., Neykova, N. A. : *J. Med. Chem.*, **23**, 1048 (1980).
5. Beyerman, H. C., Bontekoe, J. S., Van der Burg, W.J., Veer, W. L. C. : *Rev. trav. chim.*, **73**, 109(1954).
6. Wilde, W. : Brit., **776**, 118 (1957).
7. Jones, D. H. , Slack, R., Squires, S., Woolridge, K. R. H. : *J. Med. Chem.*, **8**, 676 (1965).
8. Hazzaa, A. A. B., Labouta, I. M., Kassem, M.G. : *Arch.Pharm. Chem.*, Sci. Ed., **11 (2)**, 43, (1983).
9. Rollas, S., Büyüktimkin, S., Çevikbaş, A. : *Arch. Pharm. (Weinheim)*, **324**, 189 (1991)
10. Abdou, N. A., Amin, F. M., Mansoura. : *J. Pharm. Sci.*, **6**, 25 (1990).
11. Holla, B. S., Kalluraya, B., Sridhar, K. R. : *Curr. Sci.*, **56**, 236 (1987).
12. Goswami, B. N., Kataky, J. C.S., Baruah, J. N. : *J.Heter. Chem.*, **21**, 1225 (1984).
13. Mishra, R. K., Tewari, R. K., Srivastava, S. K., Bahel, S. C. : J. *Indian. Chem. Soc.*, **68**, 110 (1991)
14. Rollas, S., Kalyoncuoğlu, N.,Sür - Altıner, D., Yeğenoglu, Y. :*Pharmazie*, 48, 308 (1993).
15. Mhalsalkar, M. Y., Shah, M. H., Nikam, S. T, Anantanarayanan, K.G., Deliwala, C. V. : *J. Med. Chem.*, **13**, 672 (1970).
16. Mhalsalkar, M. Y., Shah, M. H., Pilankar, P. D., Nikam, S. T., Anantanarayanan, K. G., Deliwala, C. V. : *ibid.*, **14**, 1000 (1971).

17. Pathak, U. S. , Devani, M. B. , Shishoo, C. J., Shah, S. A. : Indian. *J. Chem.* , **28**, 247 (1989).
18. Emilsson, H., Selander, H. : *Acta. Pharm. Suec.*, **20**, 419 (1983).
19. Emilsson, H., Selander, H. : ibid, 24, 123 (1987).
20. Rollas, S. : M. U. J. Sci. and Tech., 3, 195 (1986).
21. Durgun, B. B., Rollas, S. : *J. Pharm. Univ. Mar.*, **7**, 107 (1991).
22. Kalyoncuoğlu, N., Rollas, S., Sür - Altıner, D., Yeğenoğlu, Y., Ang, O. : *Pharmazie*, **47**, 796 (1992).
23. Ram, V. J. , Vidyottama, D., Pieters, L. A. C., Vlietinck, A. J. : *J. Het. Chem.*, **26**, 625 (1989).
24. Ergenç, N., İlhan, E., Ötük, G. : *Pharmazie*, **47**, 59 (1992).
25. Rollas, S. : *J. Fac. Pharm. Ist.*, **17**, 155 (1981).
26. Rollas, S. : *J. Pharm. Univ. Mar.*, **2**, 1 (1986).
27. Kubota, S., Horie, K., Misra, Hemant, K., Toyooka, K., Uda, M., Shibuya, M., Terada, H. : *Chem. Pharm. Bull.*, **33** (2), 662 (1985).
28. Ciugureanu, C., Sunel, V., Budeanu, C. : *Rev. Chim.*, **37**, 756 (1986).
29. Kubota, S., Uda, M. : *Chem. Pharm. Bull.*, **20**, 2096 (1972).
30. Kubota, S., Uda, M. : *ibid.*, **21**, 1342 (1973).
31. Mohsen, A., Omar, M. E., Osman, S. A. : *Pharmazie*, **28**, 30 (1973).
32. Blackman, A. J., Bowie, J. H. : *Aust. J. Chem.*, **25**, 335 (1972).
33. Ueda, T., Takada, A., Takahashi, K., Ueda, F. : *Chem. Pharm. Bull.*, **19**, 1990 (1971).

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