SYNTHESIS OF 5-METHYL-2-[2-METHYL/PHENYLIMINO-3-(3-METHYL-5-STYRYL-ISOXAZOL-4-YL)-2,3-DIHYDRO-THIAZOLE-4-CARBONYL]-2,4-DIHYDRO-PYRAZOL-3-ONES, 1,3,4-OXADIAZOLES AND 4-OXO-THIAZOLIN-5-YLIDENE-ACETIC ACID METHYL ESTERS

E. Rajanarendar*, D. Karunakar & K. Ramu
Department of Chemistry, Kakatiya University, Warangal – 506 009, India.

Abstract : Isoxazolyl thioureas **2** on reaction with ethyl bromopyruvate give methyl/phenyl [4-carboethoxy-3-(3-methyl-5-styryl-isoxazol-4-yl)3H-thiazol-2-ylidene]amines **3**, which on treatment with hydrazine hydrate affords corresponding acid hydrazides **4**. The acid hydrazides **4** on cyclocondensation with ethyl acetoacetate and triethyl orthoformate separately results in 5-methyl-2-[2-methyl/phenylimino-3-(3-methyl-5-styryl-isoxazol-4-yl)-2,3-dihydro-thiazole-4-carbonyl]-2,4-dihydropyrazol-3-ones **5** and 2-[2-methyl/phenylimino-3-(3-methyl-5-styryl-isoxazol-4-yl)-2,3-dihydro-thiazole-4-yl]-1,3,4-oxadiazoles **6** respectively. Compounds **2** on refluxing with dimethyl acetylene dicarboxylate in dry benzene underwent cyclization to give [3-(3-methyl-5-styryl-isoxazol-4-yl)-4-oxo-2-methyl/phenylimino-thiazolidin-5-ylidene]acetic acid methyl esters **7**. The structures of **4, 5, 6** and **7** are supported by spectral and analytical data.

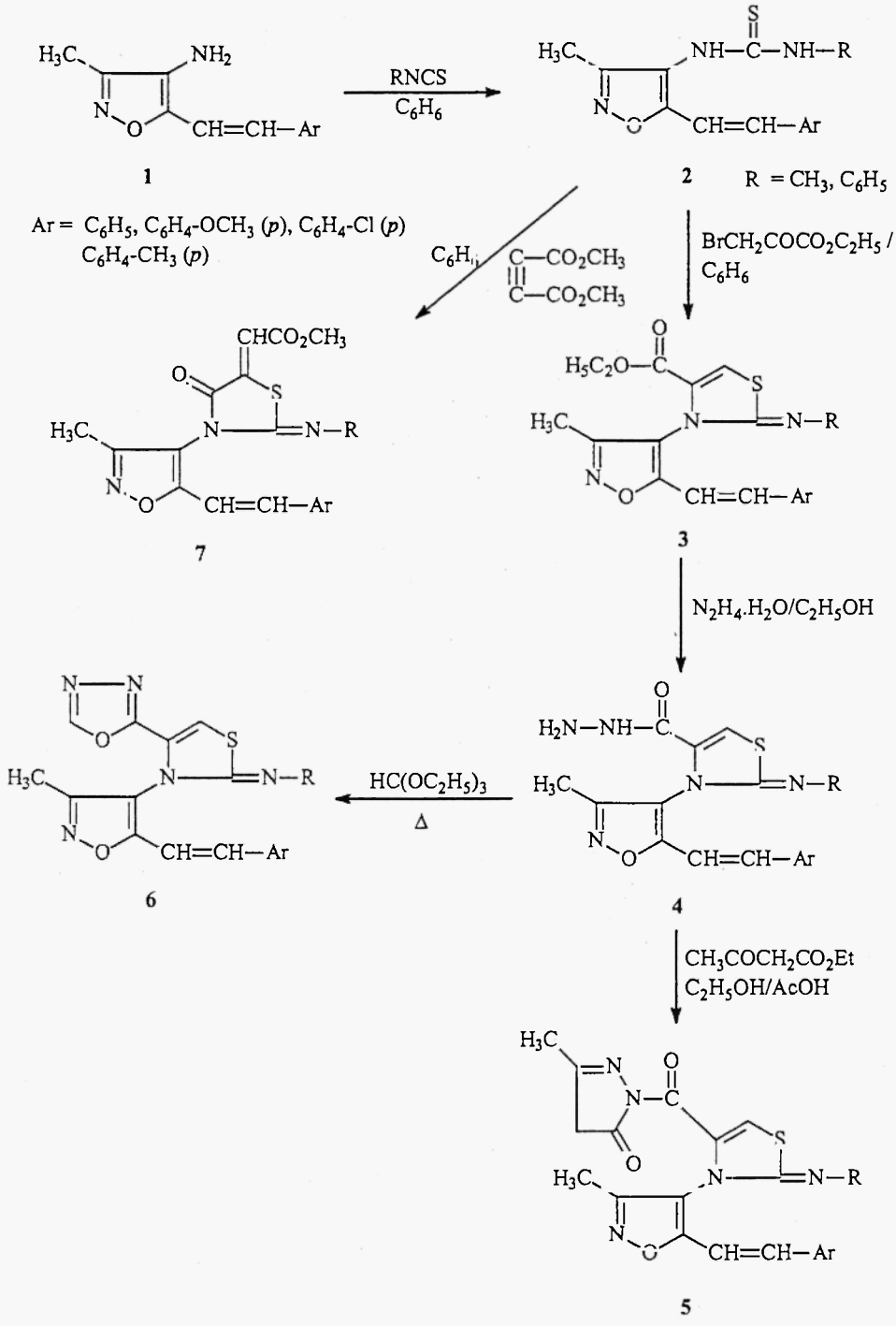
Introduction

Compounds bearing the isoxazle moiety are endowed with various types of biological activities[1-3]. A large number of pyrazolidinones are reported to possess anti-inflammatory[4] and antihistamic[5] activity. Thiazolidinone derivatives are well-known in medicinal chemistry due to their diverse pharmacological action such as anticonvulsant[6], cardiovascular[7] and antihelminthic[8] properties. Similar 1,3,4-oxadiazoles are endowed with antitubercular[9], antiviral[10] and amoebicidal[11] activities. Literature survey revealed that when one biodynamic heterocyclic system was coupled with another, a molecule with enhanced biological activity[12,13] was produced. In view of these reports and also in continuation of work on bisheterocycles[14] and trihetercycles[15] containing one of the heterocycle as isoxazole moiety, we thought of linking various heterocycles to isoxazole moiety leading to the synthesis of hitherto unknown bi and tri-heterocycles (Scheme-1) with enhanced biological activities.

Results and Discussions

The starting material, 1-methyl/phenyl(3-methyl-5-styryl-4-isoxazolyl) thioureas[14] **2** were secured by reacting 4-amino-3-methyl-5-styrylisoxazoles with methyl/lphenyl isothiocyanate in refluxing dry benzene. These thioureas **2** was reacted with ethyl bromopyruvate in dry benzene to give methyl/phenyl [4-carboethoxy-3-(3-methyl-5-styryl- isoxazol-4-yl)-3H-thiazol- 2-ylidene]amines[15] **3**. When **3** was heated with hydrazine hydrate in refluxing ethanol, it produced 2-methyl/phenylimino- 3 -(3 -methyl-5-styryl-isoxazol-4-yl)-2,3-dihydro-thiazole-4-carboxylic acid hydrazide **4** in 80% yields. IR spectrum of 4 showed absorption bands at 3401, 3370, 1690 and 1618 cm-I due to amine, carbonyl and C=N functional groups respectively. ^{1}H NMR spectrum of 4 displayed amide NH proton as a broad singlet at δ 9.8 and NH_2 protons appeared as broad signal at δ 4.6 which are D_2O exchangeable. The mass spectrum of **4** supported the structure by showing molecular ion peak at m/z 355 and M+2 peak at m/z 357.

The carbohydrazide **4** on cyclocondensation with ethyl acetoacetate in the presence of drops of acetic acid in refluxing ethanol led to the formation of 5-methyl-2-[2-methyl/phenylimino-3-(3-methyl-5-styryl-isoxazolyl-4-yl)-2,3-dihydro-thiazole-4-carbonyl]-2,4-dihydro-pyrazol-3-one 5 in good yields (70-80%). IR spectrum of **5** showed strong absorption at 1725 and 1610 cm^{-1} due to carbonyl group of pyrazolone ring and C=N functional groups. ^{1}H NMR spectrum of **5** showed two sharp singlets at δ 3.7 and 2.5 due to methylene and methyl protons of the newly formed pyrazolidinone ring confirming the cyclization. The mass spectrum of **5** showed molecular ion at m/z 421 confirming cyclocondensation.



1 2 3 4 5 6 7

The acid hydrazide **5** was further reacted separately by heating with triethyl orthoformate to afford 2-[2-methyl/phenylimino-3-(3-methyl-5-styrylisoxazol-4-yl)-2,3-dihydro-thiazol-4-yl]-1,3,4-oxadiazole **6** whose structure was established on the basis of elemental analysis and spectral data. IR spectrum of **6** did not show absorptions at 3401, 3370 due to NH_2/NH which are present in its precursor indicating cyclisation. Similarly in ^{1}H NMR spectrum of **6** the signals due to CONH and NH_2 protons at δ 9.8 and 4.6 are absent (present in its precursor) confirming the 1,3,4-oxadiazole formation by showing a lone proton signal of the newly formed ring hydrogen at δ 8.4. The mass spectrum very well agrees with the proposed structure by showing molecular ion at m/z 365 (M^+).

The isoxazolyl thioureas **2**, on cyclocondensation with dimethyl acetylene dicarboxylate (DMAD), in dry benzene led to the formation of [3-(3-methyl-5-styryl- isoxazol-4-yl)-4-oxo-2-methyl/phenylimino-thiazolidin-5-ylidene]-acetic acid methyl esters **7** in 60-70% yields. IR spectrum of **7** exhibited ester carbonyl, thiazolidinone ring carbonyl absorptions at 1727 and 1704 cm^{-1} respectively. ^1H NMR spectrum of **7** did not show signals due to NH protons (present in its precursor), but displayed two sharp singlets at δ 3.5 and 7.0 due to methyl protons of ester and olefinic proton attached to ester group. Mass spectrum of **7** showed molecular ion peak at m/z 383 confirming cyclocondensation.

In conclusion, we have accomplished the synthesis of bi and tri-heterocyclic compounds carrying thiazole, pyrazole and oxadiazole moieties on isoxazole nucleus from readily available chemicals and by simple methods which ended up with excellent yields. The biological activity of these compounds will be published elsewhere.

Experimental

Thin layer chromatography was used to access the reactions and the purity of products. Melting points were determined on a Cintex melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Perkin Elmer BX series FT-IR spectrometer, ^1H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal standard. Mass spectra were recorded on a Jeol-D-300 mass spectrometer. C, H and N analyses were carried out on a Carlo Erba 106 and Perkin-Elmer Model 240 analysers.

Preparation of 1-methyl/phenyl-3-(3-methyl-5-styryl-4-isoxazolyl)thioureas[14] 2.

4-Amino-3-methyl-5-styrylisoxazole (0.01 mole) and methyl/phenyl isothiocyanate (0.01 mole) were refluxed in dry benzene (20 mL) for 4 hrs. The reaction mixture was cooled, filtered, washed thoroughly with benzene and dried. The solid thus obtained was purified by crystallization from benzene.

Preparation of methyl/phenyl-[4-carboethoxy-3-(3-methyl-5-styryl-isoxazol-4-yl)3H-thiazol-2-ylidene]amines[15] 3

A mixture of 2 (0.01 mole) and bromo ethylpyruvate (0.01 mole) in dry benzene (20 mL) was refluxed for 4 hr. The solid separated on cooling was filtered and crystallized from benzene-ethyl acetate.

Preparation of 2-methyl/phenylimino-3-(3-methyl-5-styryl-isoxazol-4-yl)-2,3-dihydro-thiazole-4-carboxylic acid hydrazides 4

A mixture of **3** (0.01 mole) and hydrazine hydrate (99%, 0.01 mole) in ethanol (25 mL) was refluxed for 5 hr. The contents are cooled, poured in ice-water, separated solid was filtered and recrystallized from aq. Methanol. Physical and analytical data included in Table-1.

Preparation of 5-methyl-2-[2-methyl/phenylimino-3-(3-methyl-5-styryl-isoxazol-4-yl)-2,3-dihydro-thiazole-4-carbonyl-2,4-dihydro-pyrazol-3-ones 5

A mixture of acid hydrazide **4** (0.01 mole), ethyl acetoacetate (0.01 mole) and drops of acetic acid was taken in absolute alcohol (20 mL) and refluxed for 6 hr on water bath. The solid separated on cooling was-filtered and crystallized from ethanol. Physical and analytical data included in Table-1.

Table 1: Physical and analytical data of 4 and 5

Compd.	Ar	R	m.p. (°C)	Yield (%)	Mol. formula	Found (%) (Calcd)		
						C	H	N
4a	C_6H_5	CH_3	175	85	$C_{17}H_{17}N_5O_2S$	51.55 (57.46	4.81 4.78	19.75 19.71)
4b	C_6H_4-OCH_3(*p*)	CH_3	190	80	$C_{18}H_{19}N_5O_3S$	56.18 (56.10	4.95 4.93	18.20 18.18)
4c	C_6H_4-CH_3(*p*)	C_6H_5	182	90	$C_{18}H_{19}N_5O_2S$	58.55 (58.37	5.16 5.14	18.99 18.97)
4d	C_6H_4-Cl (*p*)	CH_3	197	80	$C_{17}H_{16}N_5O_2SCl$	52.39 (52.37	4.12 4.10	18.00 17.97)
4e	C_6H_5	C_6H_5	132	90	$C_{22}H_{19}N_5O_2S$	63.29 (63.30	4.51 4.55	16.69 16.78)
4f	C_6H_4-OCH_3(*p*)	C_6H_5	156	80	$C_{23}H_{21}N_5O_3S$	61.73 (61.74	4.65 4.69	15.60 15.65)
4g	C_6H_4-CH_3(*p*)	C_6H_5	141	90	$C_{23}H_{21}N_5O_2S$	64.08 (64.03	4.91 4.87	16.29 16.24)
4h	C_6H_4-Cl (*p*)	C_6H_5	163	85	$C_{22}H_{18}N_5O_2SCl$	58.50 (58.47	4.00 3.98	15.48 15.50)
5a	C_6H_5	CH_3	85	75	$C_{21}H_{19}N_5O_3S$	60.01 (59.85	4.52 4.51	16.66 16.62)
5b	C_6H_4-OCH_3(*p*)	CH_3	102	80	$C_{22}H_{21}N_5O_4S$	58.57 (58.53	4.66 4.65	15.61 15.52)
5c	C_6H_4-CH_3(*p*)	C_6H_5	93	75	$C_{22}H_{21}N_5O_3S$	60.72 (60.68	4.80 4.82	16.05 16.09)
5d	C_6H_4-Cl (*p*)	CH_3	114	70	$C_{21}H_{18}N_5O_3SCl$	55.30 (55.32	4.01 3.95	15.31 15.36)
5e	C_6H_5	C_6H_5	126	75	$C_{26}H_{21}N_5O_3S$	64.60 (64.59	4.33 4.34	14.51 14.49)
5f	C_6H_4-OCH_3(*p*)	C_6H_5	149	80	$C_{27}H_{23}N_5O_4S$	63.18 (63.15	4.50 4.48	13.69 13.64)
5g	C_6H_4-CH_3(*p*)	C_6H_5	137	75	$C_{27}H_{23}N_5O_3S$	65.21 (65.19	4.63 4.62	14.06 14.08)
5h	C_6H_4-Cl (*p*)	C_6H_5	154	70	$C_{26}H_{20}N_5O_3SCl$	60.22 (60.28	3.85 3.86	13.60 13.52)

Preparation of 2-[2-methyl/phenylimino-3-(3-methyl-5-styryl-isoxazol-4-yl)-2,3-dihydro-thiazol-4-yl]-1,3,4-oxadiazoles 6

Triethyl orthoformate (10 mL) was added to acid hydrazide **4** (0.01 mole) and heated at reflux for 10 hr. The excess of triethyl orthoformate was removed under reduced pressure and the residue was processed with pet. ether followed by methanol. The resulting solid was filtered, and crystallized from benzene. Physical and analytical data included in Table-2.

Preparation of [3-(3-methyl-5-styryl-isoxazol-4-yl)-4-oxo-2-methyl/phenylimino-thiazolidin-5-ylidene]-acetic acid methyl ester 7

To a solution of isoxazolyl thiourea **2** (0.01 mole) in dry benzene (20 mL) was added dimethyl acetylene dicarboxylate (0.01 mole). The reaction mixture was refluxed for 4 hr. The separated solid was filtered and recrystallized from benzene-ethyl acetate. Physical and analytical data included in Table-2.

Table 2 : **Physical and analytical data of 6 and 7**

Compd.	Ar	R	m.p. (°C)	Yield (%)	Mol. formula	Found (%) (Calcd)		
						C	H	N
6a	C_6H_5	CH_3	110	60	$C_{18}H_{15}N_5O_2S$	59.19 (59.17	4.11 4.10	19.15 19.17)
6b	C_6H_4-OCH_3(*p*)	CH_3	137	50	$C_{19}H_{17}N_5O_3S$	57.80 (57.72	4.31 4.30	17.75 17.72)
6c	C_6H_4-CH_3(*p*)	C_6H_5	129	55	$C_{19}H_{17}N_5O_2S$	60.16 (60.15	4.49 4.48	18.49 18.46)
6d	C_6H_4-Cl (*p*)	CH_3	144	40	$C_{18}H_{14}N_5O_2SCl$	54.09 (54.06	3.49 3.50	17.55 17.52)
6e	C_6H_5	C_6H_5	151	55	$C_{23}H_{17}N_5O_2S$	64.65 (64.63	4.00 3.98	16.41 16.39)
6f	C_6H_4-OCH_3(*p*)	C_6H_5	169	45	$C_{24}H_{19}N_5O_3S$	63.00 (63.01	4.18 4.15	15.37 15.31)
6g	C_6H_4-CH_3(*p*)	C_6H_5	162	50	$C_{24}H_{19}N_5O_2S$	65.33 (65.30	4.31 4.30	15.88 15.87)
6h	C_6H_4-Cl (*p*)	C_6H_5	178	45	$C_{23}H_{16}N_5O_2SCl$	59.87 (59.80	3.48 3.46	15.20 15.16)
7a	C_6H_5	CH_3	156	80	$C_{19}H_{17}N_3O_4S$	59.62 (59.53	4.42 4.43	10.99 10.96)
7b	C_6H_4-OCH_3(p)	CH_3	176	75	$C_{20}H_{19}N_3O_5S$	58.20 (58.11	4.55 4.60	10.12 10.16)
7c	C_6H_4-CH_3(p)	C_6H_5	164	80	$C_{20}H_{19}N_3O_4S$	60.50 (60.45	4.82 4.78	10.55 10.57)
7d	C_6H_4-Cl (p)	CH_3	187	70	$C_{19}H_{16}N_3O_4SCl$	54.60 (54.61	3.81 3.83	10.01 10.05)
7e	C_6H_5	C_6H_5	70	75	$C_{24}H_{19}N_3O_4S$	64.82 (64.71	4.30 4.26	9.45 9.43)
7f	C_6H_4-OCH_3(p)	C_6H_5	96	70	$C_{25}H_{21}N_3O_5S$	63.09 (63.15	4.40 4.42	8.91 8.84)
7g	C_6H_4-CH_3(p)	C_6H_5	82	75	$C_{25}H_{21}N_3O_4S$	65.33 (65.33	4.56 4.57	9.10 9.15)
7h	C_6H_4-Cl (p)	C_6H_5	107	70	$C_{24}H_{18}N_3O_4SCl$	60.02 (60.06	3.71 3.75	8.77 8.75)

Spectra of Representative Compounds

4a: IR (KBr) : 1618 (C=N), 1690 (-CO-), 3401 and 3370 cm-1 (NH/NH_2) ; ^1H NMR (200 MHz, DMSO-d_6) : δ 2.1 (s, 3H, isoxazole CH_3), 3.6 (s, 3H, =N-CH_3), 4.6 (bs,. 2H, NH_2, disappeared on shaking with D_2O), 6.7 (s, IH, olefinic H of thiazole moiety), 6.9 (d, IH, -CH=CH-), 7.1 (d, IH, -CH=CH-), 7.2 -7.7 (m, 5H, Ar-H), 9.8 (bs, IH, CONH,. disappeared on shaking with D_2O); MS : m/z 355 (M^+), 357 (M+2), 341, 326, 298, 233, 219, 114; **4h** : IR (KBr) : 1620 (C=N), 1680 (-CO), 3395, 3368 cm-l (NH/NH_2); ^1H NMR (200 MHz, DMSO-d_6) : δ 2.2 (s, 3H, isoxazole CH_3), 4.5 (bs, 2H, NH_2, D_2O exchangeable), 6.8 (s, IH, olefinic H of thiazole), 6.9 (d, IH, CH=CH), 7.1 (d, IH, -CH=CH-), 7.2 - 8.0 (m, 9H, ArH), 10.0 {bs, IH, CONH, D_2O exchangeable); MS : m/z 452 (M^+).

5a : IR (KBr) : 1610 (C=N), 1725 (-CO-) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) : δ 2.2 (s, 3H, isoxazole CH_3), 2.4 (s 3H, pyrazole CH_3), 3.8 (s, 3H, C=N-CH_3), 3.7 (s, 2H, CH_2), 6.7 (d, IH, CH=CH), 7.0 (s, IH, thiazole H), 7.1-7.6 (m, 6H, Ar-H, -CH=CH-); MS : m/z 421 (M^+), 423 (M+2), 408, 370, 356, 338, 242, 223, 157, 131, 99; **5e**: IR (KBr): 1615 (C=N), 1720 (-CO) cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$) : δ 2.2 (s, 3H, isoxazole CH_3), 2.4 (s, 3H, pyrazole CH_3), 3.6 (s, 2H, CH_2), 6.6 (d, IH, CH=CH), 6.9 (s, IH, thiazole -H), 7.0 -7.7 (m, 11H, Ar-H & -CH=CH-), MS : m/z 483 (M^+).

6a : IR (KBr) : 1620 (C=N) cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$) : δ 2.2 (s, 3H, isoxazole CH_3), 3.8 (s, 3H, C=N-CH_3), 7.0 (s, 1H, thiazole-H), 6.8 (d, 1H, CH=CH), 7.1 - 7.8 (m, 6H, Ar-H & -CH=CH-), 8.4 (s, 1H, oxadiazole-H); MS : m/z 365 (M^+) 367 (M+2); **6f** : IR (KBr) : 1625 (C=N) cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$) : δ 2.2 (s, 3H, isoxazole CH_3), 3.7 (s, 3H, OCH_3), 7.1 (s, 1H, thiazole-H), 6.7 (d, 1H, CH=CH-), 7.2 - 7.8 (m, 10H, Ar-H & -CH=CH-), 8.5 (s, 1H, oxidazole-H); MS : m/z 457 (M^+), 459 (M+2).

7a: IR (KBr) : 1727 (-CO-O-), 1704 (-CO-), 1640 cm^{-1} (C=N); ^1H NMR (200 MHz, $CDCl_3$) : δ 2.2 (s, 3H, isoxazole CH_3), 3.5 (s, 3H, C=N-CH_3), 3.8 (s, 3H, -$COOCH_3$), 6.6 (d, 1H, CH=CH), 7.0 (s, 1H, -C=CH), 7.2-7.6 (m, 6H, Ar-H and -CH=CH-), MS : m/z 383 (M^+), 385 (M+2), 356, 342, 319, 307, 289, 211, 154, 137, 120, 107, 89, 77, 55; **7e** : IR (KBr) : 1728 (-CO-O-), 1700 (-CO-), 1645 (C=N) cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) : δ 2.2 (s, 3H, isoxazole CH_3), 3.8 (s, 3H, $COOCH_3$), 6.7 (d, 1H, CH=CH-), 7.0 (s, 1H, -C=CH), 7.2 - 8.0 (m, 11H, Ar-H & -CH=CH-), MS : *m/z* 445 (M^+)

Acknowledgements

The authors thanks Director, IICT, Hyderabad for the ^1H NMR and mass spectral data and CIC, Kakatiya University, Warangal for the IR spectra. One of the authors (DK) acknowledge the financial support of the CSIR, New Delhi.

References

1. Getal, J. Antibiot., **28(1)**, 91 (1975).
2. G.D. Diana, M.A. Mckinlay, M.J. Otto, V. Akyllian, R.C. Oglesby, J. Med. Chem., **28**, 1906 (1985).
3. S. Batra, T. Srinivasan, S.K. Rastogi, B. Kundu, A. Patra, A.P. Bhaduri, M. Dixit, Biorg. Med. Chem. Lett., **12**, 1905 (2002).
4. K.H. Kym, C. Yvoune, B. Norris, D.R. Young, G.W. Caster, F. Haviv, R.L. Walten, J. Pharma. Sci., **79**, 609.
5. G. Achaiah, R. Raja Reddy, Y. Jayamma, V.M. Reddy, Indian J. Pharm. Sci., **53**, 197 (1991).
6. C. Dwivedi, T.K. Gupta, S.S. Parmar, J. Med. Chem., **16**, 178 (1973).
7. S.P. Singh, S.K. Anyyoung, S.S. Parmar, J. Pharm. Sci., **63**, 960 (1974).
8. M.J. Hussaian, S.K. Agarwal, Indian J. Pharm. Sci., **37**, 89 (1995).
9. J.J. Piala, H.L. Yale, US Pat. **3**, 166 (1965); Chem. Abstr., **53**, 16159 (1959).
10. N. Srivastav, S. Bahadur, H.N. Varma, M.M. Khan, Curr. Sci., **53**, 235 (1984).
11. C. Andotra, T.C. Langer, S. Sharma, J. Indian Chem. Soc., **66**, 235 (1984).
12. Boschail, C. Cana, A. Disfilo, R. Frutlero, A. Gasco, Biorg. Med. Chem., **7**, 1727 (2000).
13. P. Moloney Gerard, Martin Graemer, Mathew, J. Chem. Soc. Perkin Trans., **19**, 2725 (1999).
14. E. Rajanarendar, Md. Afzal, D. Karunakar, Indian J. Chem., **42B**, 352 (2003).
15. E. Rajanarendar, D. Karunakar, M. Srinivas, Indian J. Chem., **43B**, 643 (2004).

Received on April 12, 2005.