SYNTHESIS OF 3-(N-1,3-DIARYLPYRAZOL-5-YL)AMINO-2*H*-[1,4]-BENZOXA/ TIIIAZINES AND 3-(N-1,3-DIARYLPYRAZOL-5-YL)IMINOMETHYL CHROMONES

G. Jagath Reddy*, D. Manjula and K. Srinivasa Rao
R & D Laboratories, Dr. Jagath Reddy's Heterocyclics, 81, S.V.Co-op Industrial Estate,
Balanagar, Hyderabad 500 037, India.
E-mail: jagathreddy@usa.net
and
Md. Khalilullah, D. Latha and C. Thirupathaiah
Department of Chemistry, Jawaharlal Nehru Technological University, Hyderabad 500 072, India.

Abstract: A series of new 3-(N-1,3-diarylpyrazol-5-yl)amino-2*H*-[1,4]-benzoxa/ thiazines (4a-c, 5a & 6a-c) and 3-(N-1,3-diarylpyrazol-5-yl)iminomethyl chromones (8a-e) have been synthesized from 5-amino-1,3-diarylpyrazoles (1).

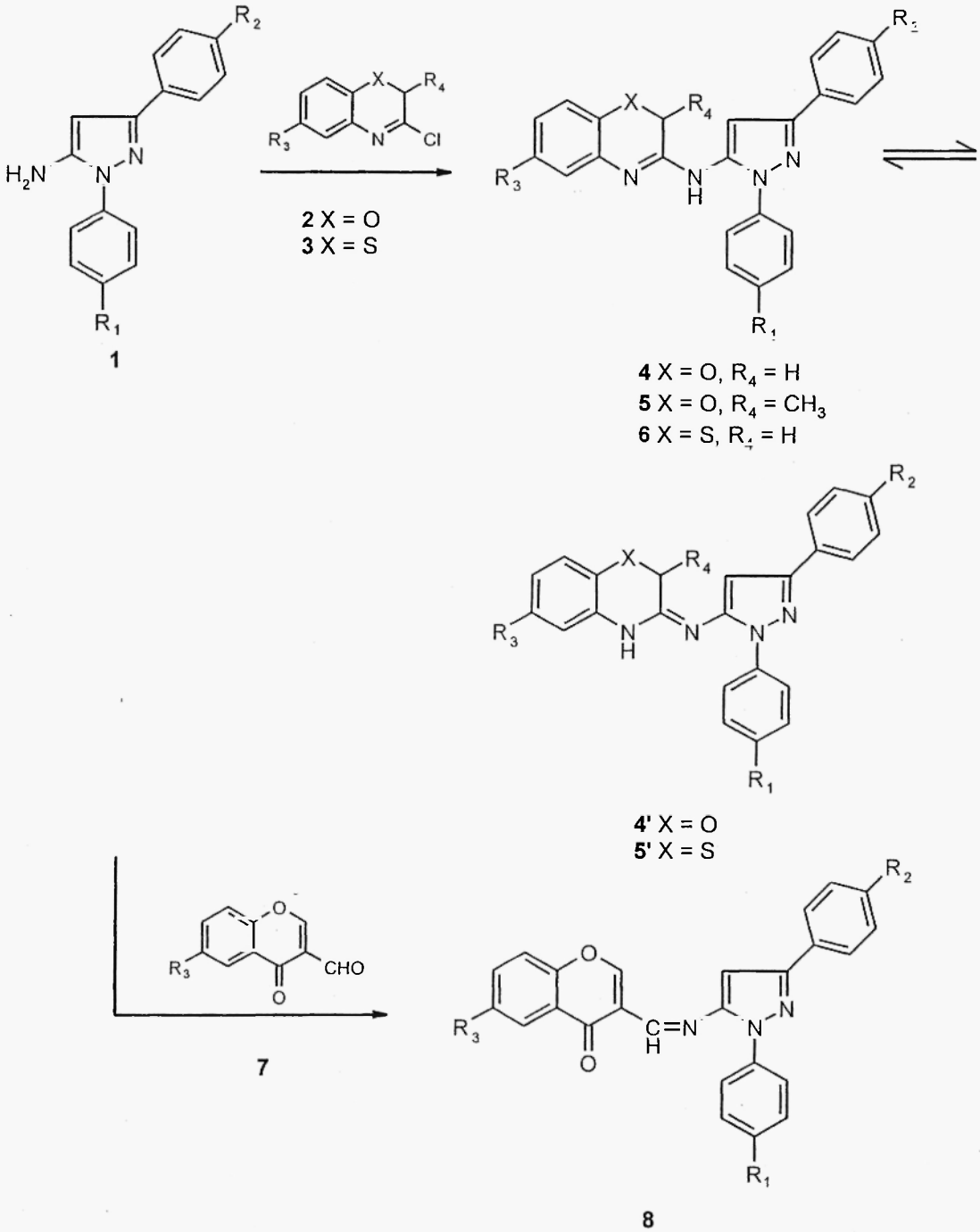
Introduction

The synthesis of heterocycles with a pyrazole nucleus has been attracting much attention because of their pharmacological interest such as antianxiety[1], antipyretic, analgesic, antiinflammatory[2] and antimicrobial[3] properties. Several arylpyrazoles have been reported as non-nucleoside HIV-1 reverse transcripatase inhibitors[4] and apoptis inducing agents useful in the treatment of prostrate cancer[5]. A number of carbamoyl pyrazoles with anticoagulant activities have also been reported[6]. Chromone moiety forms part of a number of compounds with medicinal properties like anticancer[7], neuroprotective[8] and antioxidant activities[9]. Furthermore, simple benzofused 1,4-oxazines and thiazines are receiving great attention in medicinal research as interesting pharmacophores with their presence in drugs like *Ofloxacin*[10] (antibacterial) and *Semotiadil*[11] (antihypertensive). In view of these observations and in continuation of our interest in library synthesis of pyrazoles[12], chromones[13] and benzoxa/thiazines[14], we report herein the synthesis of some new pyrazolylaminobenzoxa/thiazines **4** & **6** and pyrazolyliminomethyl chromones **8**.

Results and Discussions

Various 5-aminopyrazoles **1**, required in the present work were prepared by reaction of different benzoylacetonitriles with phenylhydrazines in refluxing isopropanol in the presence of montmorillonite MK-10 as solid acid catalyst[15]. Reaction of 3-oxobenzoxa/thiazines with phosphorousoxy chloride gave the iminochlorides[16] (**2** & **3**), which were reacted *in situ* with **1** to furnish the pyrazolylaminobenzoxa/thiazines **4**, **5** & **6** in moderate to good yields as crystalline solids. Compounds **4** & **6** exhibited signals around δ 4.7 and 3.6 for $-OCH_2$ and $-SCH_2$ protons and are in tautomeric equilibrium with **4'** & **6'** in the amidinic region[17]. Compound **5** exhibited a doublet (δ 1.58) and a quartet (δ 4.75) for $OCHCH_3$ protons.

3-Formylchromones readily react with primary aromatic amines to give a mixture of the anil and the adduct which is formed by further addition of amine to anil. Pure anils can be obtained by carrying out the reaction in the presence of *p*-toluenesuffonic acid[18]. In the present work, anils 8 were obtained in good to excellent yields by reaction of 3- formyl chromones 7 with aminopyrazoles 1 in refluxing benzene in the presence of montmorillonite MK-10. Compounds 8 exhibited characteristic signals for chromone C-2 and CH=N protons in their ^{1}H NMR spectra. The structures of the products 4 - 6 & 8 were based on their correct elemental analyses, ^{1}H-NMR, IR and Mass spectra of representative compounds (Table-1).


R2
H2N
N
N
R1
1
X
R4
R3
N
Cl
2 X = O
3 X = S
R2
X
R4
R3
N
N
H
N
N
R1
4 X = O, R4 = H
5 X = O, R4 = CH3
6 X = S, R4 = H
R2
X
R4
R3
N
H
N
N
N
R1
4' X = O
5' X = S
O
R3
CHO
O
7
R2
O
R3
C=N
H
O
N
N
R1
8

Scheme I

Table-1: Physical and spectral data of compounds **4**, **6** and **8**

Compd*	R_1	R_2	R_3	m.p. °C	Yield (%)	Mol. formula	Found (Calc.) % C	H	N	^{1}H NMR δ ppm, DMSO-d_6
4a	H	Cl	H	176-78	71	$C_{23}H_{17}ClN_4O$	68.62 (68.91	4.56 4.24	14.19 13.98)	4.73(s, 2H), 6.36(s, 1H), 6.83(m, 1H), 6.91-7.12(m, 3H), 7.36(m, 4H), 7.74-7.96(m, 5H), 8.31(bs, 1H)
4b	Cl	Cl	H	184-86	72	$C_{23}H_{16}Cl_2N_4O$	63.26 (63.44	4.01 3.67	13.16 12.87)	4.73(s, 2H), 6.38(s, 1H), 6.81(m, 1H), 6.93-7.01(m, 3H), 7.38(2d, 4H), 7.72-7.98(m, 5H)
4c	CH_3	F	Cl	204-06	69	$C_{24}H_{18}FClN_4O$	66.41 (66.58	4.43 4.16	13.27 12.94)	2.37(s, 3H), 4.71(s, 2H), 6.34(s, 1H), 6.85(m, 1H), 7.14(m, 3H), 7.34(m, 3H), 7.71-7.96(m, 4H), 8.32(bs, 1H)
5a	CH_3	H	Cl	190-92	74	$C_{25}H_{21}ClN_4O$	70.34 (70.01	5.26 4.90	12.87 13.06)	1.58(d, 3H), 2.37(s, 3H), 4.76(q, 1H), 6.36(s, 1H), 6.81(d, 1H), 6.91(d, 2H), 7.24(m, 2H), 7.41(m, 4H), 7.64(m, 3H), 8.37(bs, 1H)
5b	CH_3	CH_3	Cl	200-02	68	$C_{26}H_{23}ClN_4O$	70.19 (70.50	5.41 5.19	12.91 12.65)	1.58(d, 3H), 2.38(s, 6H), 4.75(q, 1H), 6.37(s, 1H), 6.80(m, 1H), 6.91(d, 2H), 7.24(m, 2H), 7.42(m, 4H), 7.63(m, 2H), 8.36(bs, 1H)
6a	Cl	Cl	H	214-16	67	$C_{23}H_{16}Cl_2N_4S$	61.46 (61.19	3.76 3.54	12.74 12.41)	3.62(s, 2H), 6.23(s, 1H), 6.76(dd, 1H), 6.95(m, 1H), 7.21(m, 6H), 7.48(d, 1H), 7.63(dd, 1H), 7.78(m, 2H), 8.35(bs, 1H)
6b	CH_3	F	H	198-200	73	$C_{24}H_{19}FN_4S$	69.31 (69.56	4.81 4.58	13.76 13.52)	2.36(s, 3H), 3.61(s, 2H), 6.21(s, 1H), 6.73(m, 1H), 6.96(dd, 1H), 7.23(m, 6H), 7.51(dd, 1H), 7.63(m, 1H), 7.76(m, 2H), 8.36(bs, 1H)
6c	CH_3	CH_3	H	218-20	74	$C_{25}H_{22}N_4S$	73.42 (73.17	5.17 5.36	13.78 13.65)	2.38(s, 6H), 3.60(s, 2H), 6.21(s, 1H), 6.75(dd, 1H), 6.96(dd, 1H), 7.24(m, 6H), 7.51(dd, 1H), 7.63(dd, 1H), 7.78(m, 2H), 8.37(bs, 1H)
8a	F	CH_3	H	188-90	77	$C_{25}H_{18}FN_3O_2$	61.73 (61.46	4.61 4.25	10.14 9.92)	2.44(s, 3H), 6.93(s, 1H), 7.13-7.36(m, 5H), 7.51-7.64(m, 2H), 7.94(d, 2H), 8.23(m, 2H), 8.65(d, 1H), 8.96(d, 1H), 11.91(s, 1H)
8b	CH_3	CH_3	H	186-88	78	$C_{27}H_{21}N_3O_2$	73.67 (73.32	4.87 5.01	10.21 10.00)	2.44(s, 6H), 6.94(s, 1H), 7.14(d, 1H), 7.38(2d, 4H), 7.52-7.65(2dd, 2H), 7.94(d, 2H), 8.21(d, 2H), 8.66(d, 1H), 8.98(d, 1H), 11.91(s, 1H)

Table-1 (continued): Physical and spectral data of compounds **4**, **6** and **8**

Compd*	R_1	R_2	R_3	m.p. °C	Yield (%)	Mol. formula	Found (Calc.) % C	H	N	^{1}H NMR δ ppm, DMSO-d_5
8c	F	CH_3	CH_3	204	76	$C_{27}H_{20}FN_3O_2$	74.51 (74.14	4.73 4.57	9.78 9.61)	2.43(s, 3H), 2.48(s, 3H), 6.92(s, 1H), 7.21-7.37(m, 5H), 7.52-7.64(m, 2H), 7.95(d, 2H), 8.19(d, 1H), 8.63(d, 1H), 8.93(d, 1H), 11.90(s, 1H)
8d	F	CH_3	F	202	74	$C_{26}H_{17}F_2N_3O_2$	70.58 (70.74	4.18 3.85	9.41 9.52)	2.45(s, 3H), 6.94(s, 1H), 7.23-7.38(m, 4H), 7.51-7.62(m, 2H), 7.88(dd, 2H), 8.19(d, 2H), 8.62(d, 1H), 8.82(d, 1H), 11.91(s, 1H)
8e	F	CH_3	Cl	228	72	$C_{26}H_{17}ClFN_3O_2$	68.23 (68.19	4.06 3.71	9.45 9.18)	2.44(s, 3H), 6.93(s, 1H), 7.23-7.39(m, 4H), 7.53-7.64(m, 2H), 7.87(d, 2H), 8.21(dd, 2H), 8.64(d, 1H), 8.92(d, 1H), 11.93(s, 1H)

Experimental Section

Melting points were determined in open capillaries and are uncorrected. The purity of all the compounds was routinely checked by TLC on silica gel coated plates. IR spectra were recorded on KBr pellets on a Perkin Elmer System 2000 FT-IR spectrometer. ^{1}H NMR spectra on a Varian 200 MHz instrument with TMS as internal standard and chemical shifts expressed in δ ppm. Mass spectra were recorded on Hewelett Packard mass spectrometer operating at 70 eV.

General procedure for the preparation of 3-(N-1,3-diarylpyrazol-5-yl)amino-2*H*-[1,4]-benzoxa/thiazines (4–6). To a mixture of 3-oxo-3,4-dihydro-2*H*-1,4-benzoxa/thiazine (0.01 mol) in dichloroethanone (10 mL), phosphorous oxychloride (0.015 mol) was added drop wise at room temperature and stirred for 30 min. It was cooled to 5°C, triethylamine (0.2 mol) was added drop wise, followed by addition of 1,3-diarylpyrazol-5-amine (0.01 mol) dissolved in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 1 hr, followed by refluxing for 5-6 hr. At the end of the reaction as monitored by TLC (Hexane, ethylacetate in the ratio 8:2) it was poured onto crushed ice, organic layer extracted with dichloroethane (2 x 25 mL), washed with water, dried (Na_2SO_4), solvent removed and subjected to flash column chromatography and eluted with 10% ethylacetate : hexane to give pure **4-6** as light yellow crystalline solids.

The physical and spectral data of **4-6** thus prepared are listed in **Table-1**.

General procedure for the preparation of 3-(N-1,3-diarylpyrazol-5-yl)iminomethyl chromones 8. A mixture of 3-formylchromone **6** (0.01 mol), 5-amino-1,3-diarylpyrazole (0.01 mol), dry benzene (50 mL) montmorillonite MK-10 was heated under reflux, till the absence of starting materials as followed by TLC and the resulting mixture was filtered hot, solvent removed and the resulting solid was recrystallized from benzene to pure **8** as light yellow crystalline solids.

The physical and spectral data of **8a-e** thus prepared are listed in **Table-1**.

References

1. D. J. Wustrow, T. Capiris, R. Rubin, J. A. Knobelsdorf, H. Akunne, M. D. Davis, R. Mac Kenzie, T. A. Pugdey, K. T. Zoski, T. G. Heffner, L. D. Wise, *Bioorg. Med Chem Lett* **8**, 2067 (1998).
2. T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecham J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, P. C. Isakson, *J Med Chem.* **40**, 1347 (1997).
3. G. Daidone, B. Maggio, S. Plescia, D. Raffa, C. Musiu, C. Milia, G. Perra, Marongiu, *Eur. J Med Chem.* **33**, 375 (1998).
4. M. J. Genin, C. Biles, B. J. Keiser, S. M. Poppe, S. M. Swaney, W. G. Tanplay, Y. Yagi, D. I. Romero, *J Med Chem.* **43**, 1034 (2000).
5. N. Pommery, T. Taverne, A. Telliez, L. Goossens, C. Charlier, J. Pommery, J. F. Goossens, R. Houssin, F. Durant, J. Henichart, *J Med Chem.* **47**, 6195 (2004).
6. J. R. Pruitt, D. J. P. Pinto, R. A. Galemmo, R. S. Alexander, K. A. Rossi, B. L. Wells, S. Drummond, L. L. Bostron, D. Burdik, R. Bruckmer, H. Chen, A. Smallwood, P. C. Wong, M. R. Wright, S. Bai, J. M. Luettegen, R. M. Knabb, P. Y. S. Lam, R. R. Wexler, *J Med Chem.* **46**, 5298 (2003).

7. A. Boumendjel, F. Bois, C. Beney, A. M. Mariotte, G. Conseil, A. Dipetro, *Bioorg Med Chem Lett.* **11**, 75 (2001).

8. R. Larget, B. Lockhart, P. Renand, M. Largeron, *Bioorg Med Chem Lett.* **10**, 835 (2000).

9. P. J. Pietta, *J Nat Prod.* **63**, 1035 (2000).

10. L. A. Mitscher, P. N. Sharma, D. T. W. Chu, L. L. Shen, A. G. Pernet, *J Med Chem.* **30**, 2283 (1987).

11. M. Fujita, S. Ito, A. Ota, N. Kato, K. Yamomoto, Y. Kawashima, H. Yamauchi, J. Iwao, *J Med Chem.* **33**, 1898 (1990).

12. a) G. Jagath Reddy, D. Manjula, K. Srinivasa Rao, M. D. Khalilullah, D. Latha, *Indian J Chem.* (SCCB No.321/2004) (2005).

    b) G. Jagath Reddy, K. Pallavi, R. Shailaja Reddy, K. Srinivasa Rao, *Indian J Chem*, (SCCB No.234/2004) (2004).

13. G. Jagath Reddy, D. Latha, C. Thirupathaiah, K. Srinivasa Rao, *Tetrahedron Lett.* **45**, 847 (2004).

14. K. N. Jayaveera, S. Sailaja, G. Jagath Reddy, K. Srinivasa Rao, *Heterocyclic Commun.* **11**, 105 (2005).

15. G. Jagath Reddy, D. Latha, K. Srinivasa Rao, *Org Prepn Proced Intl.* 494 (2004).

16. a) C. V. Reddy Sastry, K. Srinivasa Rao, V. S. H. Krishnan, K. Rastogi, M. L. Jain, *Synthesis* 336 (1988).

    b) P. S. N. Reddy, Pragati Reddy, G. Jagath Reddy, K. Srinivasa Rao, *Heterocclic Commun.* **10**, 163 (2004).

17. R. Barbieru, H. Hartmann, W. Grahn, D. Pratt, P. G. Janes, *Heterocycles.* **63**, 249 (2004).

18. G. Sabitha, *Aldrichim Acta.* **29**, 15 (1996).

Received on May 05, 2005.