

# Synthesis, Antiinflammatory and HIV-1 Integrase Inhibitory Activities of 1,2-Bis[5-thiazolyl]ethane-1,2-dione Derivatives

P. X. FRANKLIN, S. YERANDE, H. M. THAKAR, G. S. INAMDAR, R. S. GIRI, H. PADH<sup>1</sup>, V. SUDARSANAM<sup>1</sup> AND KAMALA K. VASU\*

Medicinal Chemistry Department, <sup>1</sup>Biotechnology Department, B. V. Patel Pharmaceutical Education and Research Development Centre, Thaltej, Ahmedabad-380 054, India

Franklin, *et al.*: New Thiazole Derivatives as Antiinflammatory and Inhibitors of HIV-1 Integrase

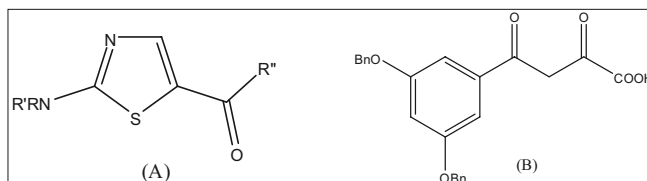
Based on principles of pharmacophore delineation and drug designing, compounds containing diketofunctionality namely 1,2-bis[5-thiazolyl]ethane-1,2-diones were designed and synthesized as antiinflammatory agents. The compounds were evaluated in carrageenan-induced rat-paw edema method. G-3, G-6, G-17, G-20, G-23, G-22, L-708 and 906 showed good antiinflammatory activity. In addition as diketo functionality containing compounds are reported to have HIV-1 integrase inhibitory property, and these compounds contains diketo functionality, so these compounds were screened in assay for HIV-1 integrase inhibition. Few compounds showed weak HIV-1 integrase Inhibitory activity.

**Key words:** N,N-diethyl benzamidine, N,N-diethyl phenylacetamidine, 1,4-dibromo butane-2,3-dione, benzoylisothiocyanate

Rheumatoid arthritis is a chronic inflammatory disorder which affects 1-2% of the total world population, commonly leads to significant disability and a consequent reduction in quality of life<sup>[1]</sup>. The available antirheumatic drugs include NSAIDs, drugs acting on cytokines and disease modifying antirheumatic drugs (DMARDs)<sup>[2]</sup>. Treatment using NSAIDs, only provide symptomatic relief. TNF- $\alpha$  is a cytokine and inhibitors of this cytokine eg. Etanercept, Infliximab and IL-1 inhibitor anakira, which act on cytokines, have demonstrated clinical efficacy in the treatment of rheumatoid arthritis. But treatments with these agents are costly and require parenteral administration<sup>[3]</sup>. Even though DMARDs (e.g., methotrexate, cyclosporine) inhibit the disease progression, the adverse effects of these drugs are very unpalatable<sup>[4,5]</sup>. The unmet medical need calls for drug discovery programs for discovery of drugs which inhibit the disease progression, which are safe and with oral bioavailability.

Our earlier drug discovery program for the treatment

of inflammatory disorders found the template of substituted 2-amino thiazol-5-yl-oxo (fig. 1A) ideal for designing drugs for inflammatory disorders<sup>[6]</sup>. There are several literature reports which highlight the fact that when 2 “minimum structural features necessary for activity” are incorporated into one single molecule the activity increases many folds<sup>[7,8]</sup>. Novel bisquinoline analogue (I) with chloroquine-like features was found to inhibit both chloroquine sensitive and resistant *P. falciparum* malarial parasites (IC<sub>50</sub> -17 nM in resistant strains as compared to chloroquine which was 540 nM)<sup>[9]</sup>. Another example is the bis-(difluoro methylene phosphonate) analogue which was more active as a protein tyrosine phosphatase 1B inhibitor as compared to the monophosphonate<sup>[10]</sup>. Literature nowadays is replete



**Fig 1:** Substituted 2-amino thiazol-5-yl-oxo and diketoaryl motifs. Templates of A. substituted 2-amino thiazol-5-yl-oxo and B. Diketoaryl motifs

\*Address for correspondence

E-mail: perd@perdcentre.com

with instances of such idea. Applying this strategy to the template we synthesized a series 1,2-bis[5-thiazolyl]ethane-1,1-diones as antiinflammatory agents.

Integrase (IN) has emerged as an attractive target, because it is necessary for stable infection and homologous enzymes are lacking in the human host<sup>[11]</sup>. The function of IN is to catalyze integration of proviral DNA, resulting from the reverse transcription of viral RNA, into the host genome. This is achieved in a stepwise fashion by endonucleolytic processing of proviral DNA within a cytoplasmic preintegration complex (termed 3' P-processing or "3'-P"), followed by translocation of the complex into the nuclear compartment where integration of 3'-processed proviral DNA into host DNA occurs in a "strand transfer" (ST) reaction. Although numerous agents potentially inhibit 3C'-P and ST in extracellular assays that employ recombinant IN and viral long terminal repeat oligonucleotide sequences, often such inhibitors lack inhibitory potency when assayed using fully assembled preintegration complexes or fail to show antiviral effects against HIV infected cells. Recently, however, a class of IN inhibitors has emerged, typified by an aryl-diketo motif. Variations of this structural theme have been utilized by Shionogi and Merck pharmaceutical companies to prepare inhibitors (for example, L-708,906) which potentially block integration in extracellular assays and exhibit good antiviral effects against HIV-infected cells. (fig. 1B)<sup>[11,12]</sup>. The presence of diketo pharmacophore in the synthesized compounds made us to screen these compounds in a HIV-1 integrase inhibitory assay.

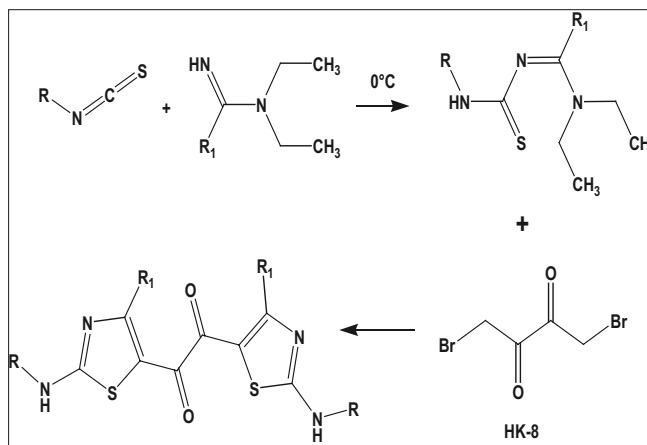
## MATERIALS AND METHODS

Phenyl isothiocyanate was procured from Lancaster. Methyl isothiocyanate was gift sample from Hitesh Chemicals and Drugs Pvt Ltd, Hyderabad, India. Benzoylisothiocyanate, methoxycarbonyl isothiocyanate, ethoxy carbonyl isothiocyanate, N,N-diethyl acetamide, N,N-diethyl benzamide, N,N-diethylphenyl acetamide and 1,4-dibromo butane 2,3-dione were prepared in our lab following the reported procedures<sup>[13-17]</sup>. Carrageenin was procured from Spectrochem India limited. HIV-1 integrase assay was done at Department of Pharmaceutical Sciences, School of Pharmacy, University of Southern California, Los Angeles, USA<sup>[18]</sup>. The reported protocol was followed for carrageenin-induced rat paw

edema method<sup>[19]</sup> for evaluation of antiinflammatory activity. All compounds were screened in a group of 6 animals at dose of 100 mg/kg body weight of the animal. The experimental protocol was approved by the institutional animal ethics committee, constituted as per CPCSEA, Government of India.

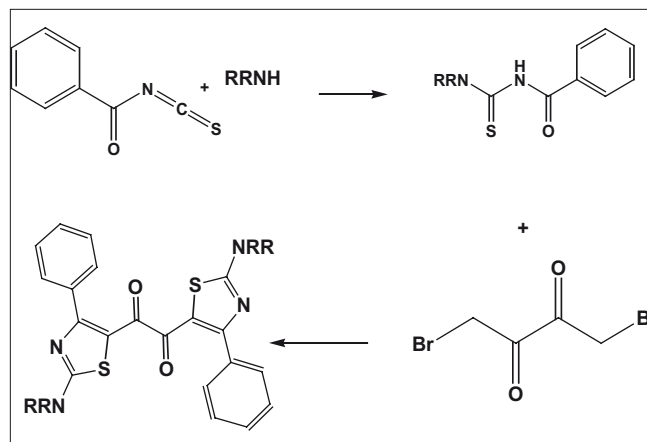
### General method of preparation of intermediates with amidines, Scheme 1:

The scheme reported by Rajappa *et al.* was utilized for the synthesis of the target molecules<sup>[20-23]</sup>. Various isothiocyanates were reacted with N,N-diethyl acetamide, N,N-diethyl benzamide, N,N-diethyl phenylacetamide to give the adducts. Some other adducts were synthesized by reacting benzoylisothiocyanate with corresponding secondary amines. The final compounds were synthesized



Scheme 1: General method of preparation of intermediates with amidines.

General method of synthesis of 1,2-bis[2-(alkylamino)-4-alkyl-1,3-thiazol-5-yl]ethane-1,2-ones



Scheme 2: General method of preparation of intermediates with secondary amines.

General method of synthesis of 1,2-bis[2-(dialkylamino)-4-phenyl-1,3-thiazol-5-yl]ethane-1,2-ones

by the reaction of 1,4-dibromo butane-2,3-dione, with the adducts. For preparation of adducts, the isothiocyanates were stirred with amidines in toluene at 0°. The solid that separated was filtered washed with cold toluene and dried.

### General method of preparation of intermediates

### with secondary amines, Scheme 2:

The solution of benzoyl chloride and ammonium thiocyanate in acetone in a round bottom flask attached with a reflux condenser, were refluxed for 15 min. To this corresponding secondary amine was added and refluxing was continued for another 2 h. After cooling the reaction mixture was poured into

**TABLE 1: PHYSICAL DATA OF SYNTHESIZED COMPOUNDS**

Code	Molecular Formula	Formula Weight	M. P. (°)	LC-MS (M+1)	IR (KBr cm <sup>-1</sup> )	NMR (δ ppm)
G-1	C <sub>12</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	310.39	*	311	3212, 2634, 1592, 1465, 1395, 1276, 1237, 1023, 809	(d <sub>6</sub> DMSO) 11.25(2H, s, 2NH), 7.09-7.63(10H m, aromatic), 2.26(12H, s, 4CH <sub>3</sub> )
G-2	C <sub>22</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	434.53	*	435	3197, 2939, 1602, 1558, 1451, 1368, 1329, 1227, 1023, 799	
G-3	C <sub>22</sub> H <sub>16</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	503.42	*	504	3173, 2930, 1611, 1560, 1494, 1467, 1425, 1369, 1337, 1232, 1211, 1096, 1012, 801	
G-4	C <sub>14</sub> H <sub>14</sub> N <sub>4</sub> O <sub>6</sub> S <sub>2</sub>	398.41	*	399	3173, 2954, 1733, 1633, 1558, 1500, 1371, 1212, 815, 760	
G-5	C <sub>16</sub> H <sub>18</sub> N <sub>4</sub> O <sub>6</sub> S <sub>2</sub>	426.46	*	427	3163, 1732, 1634, 1553, 1478, 1324, 1298, 1215, 815,	
G-6	C <sub>34</sub> H <sub>22</sub> N <sub>4</sub> O <sub>4</sub> S <sub>2</sub>	614.49	234-6	615	3314, 1675, 1644, 1522, 1454, 1409, 1330, 1298, 1223, 1099, 926, 816, 703, 659,	
G-7	C <sub>22</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	434.53	250-2	435	3184, 2989, 1682, 1658, 1441, 1358, 1339, 1220, 1023, 760	
G-8	C <sub>32</sub> H <sub>22</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	558.67	>265	559	1622, 1600, 1557, 1508, 1451, 1431, 1431, 1335, 1279, 1211, 939, 802, 771, 755,	(d <sub>6</sub> DMSO) 11.06(2H, s, 2NH), 7.10-7.95(20H m, aromatic)
G-9	C <sub>32</sub> H <sub>20</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	627.56	*	628	1621, 1515, 1497, 1453, 1335, 1277, 1235, 1073, 794, 770,	
G-10	C <sub>24</sub> H <sub>18</sub> N <sub>4</sub> O <sub>6</sub> S <sub>2</sub>	522.55	*	523	3345, 1753, 1659, 1528, 1513, 1465, 1336, 1327, 1214, 1198, 754,	
G-11	C <sub>26</sub> H <sub>22</sub> N <sub>4</sub> O <sub>6</sub> S <sub>2</sub>	550.60	252-5	551	3335, 1745, 1639, 1531, 1504, 1455, 1326, 1307, 1224, 1195, 804	
G-12	C <sub>34</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	586.72	*	587	1609, 1555, 1539, 1476, 1450, 1361, 1312, 1156, 985, 804, 776	
G-13	C <sub>34</sub> H <sub>24</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	655.61	261-3	656	3176, 3035, 1603, 1552, 1494, 1458, 1408, 1355, 1230, 1089, 828, 716	
G-14	C <sub>26</sub> H <sub>22</sub> N <sub>4</sub> O <sub>6</sub> S <sub>2</sub>	550.60	*	551	3178, 3036, 2954, 1738, 1645, 1558, 1480, 1339, 1208, 1072, 814, 765,	
G-15	C <sub>28</sub> H <sub>26</sub> N <sub>4</sub> O <sub>6</sub> S <sub>2</sub>	578.66	*	579	3329, 1742, 1632, 1540, 1465, 1197, 1058, 799,	
G-16	C <sub>36</sub> H <sub>26</sub> N <sub>4</sub> O <sub>4</sub> S <sub>2</sub>	642.74	*	643	3315, 3029, 1682, 1632, 1542, 1469, 1406, 1356, 1295, 1215, 1093, 898, 806, 690	
G-17	C <sub>30</sub> H <sub>30</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	542.71	235 d	543	2939, 1663, 1606, 1552, 1465, 1446, 1281, 940, 774	
G-18	C <sub>28</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	546.66	155-7	547	1646, 1609, 1579, 1486, 1456, 1354, 1293, 1180, 929, 702,	
G-19	C <sub>30</sub> H <sub>32</sub> N <sub>6</sub> O <sub>2</sub> S <sub>2</sub>	572.74	220 d	573	3421, 2944, 1733, 1697, 1683, 1661, 1638, 1532, 1300, 1205, 1076, 950, 780	
G-20	C <sub>32</sub> H <sub>36</sub> N <sub>6</sub> O <sub>2</sub> S <sub>2</sub>	600.79	198-200	601	3173, 2983, 2837, 1689, 1601, 1580, 1539, 1489, 1464, 1430, 1385, 1365, 1314, 1284, 1259, 1230, 1138, 1021, 722, 660	
G-21	C <sub>40</sub> H <sub>36</sub> N <sub>6</sub> O <sub>2</sub> S <sub>2</sub>	696.88	189-90	697	1663, 1619, 1533, 1498, 1456, 1350, 1350, 1326, 1294, 1227, 1026, 1001, 936, 770	
G-22	C <sub>42</sub> H <sub>40</sub> N <sub>6</sub> O <sub>2</sub> S <sub>2</sub>	724.93	178-80	725	1688, 1600, 1532, 1264, 1228, 1153, 1117, 939, 865, 700	

\*Indicates that these compounds have melting point higher than 300°

excess ice cold water. The solid that separated was filtered and dried to obtain the intermediates.

#### Preparation of 1,4-dibromo butane-2,3-dione<sup>[24]</sup>:

1,4-Dibromo butane-2,3-dione was prepared by modification of a reported method. In a three necked round bottomed flask, 10 ml  $\text{CHCl}_3$  was taken. In separating funnels diacetyl (20 g, 0.23 mol) and bromine (37.2 g, 0.46 mol) were taken in 50 and 30 ml  $\text{CHCl}_3$ , respectively. Both the solutions were added drop wise simultaneously into the flask by keeping a little excess of bromine in the flask throughout the addition. Disappearance of bromine colour was observed during the reaction. The orange colour solution was kept at  $0^\circ$  for 8 h. The solid that separated was filtered. The filtrate was washed with  $\text{NaHCO}_3$  solution dried and concentrated to get II crop 1,4-dibromo butane-2,3-dione. Yield 71%, mp  $170^\circ$ .

#### General procedure for synthesis of the final compounds:

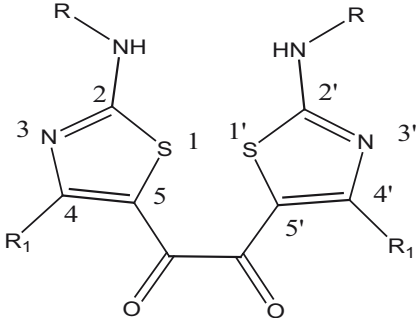
Two equivalents of adduct and one equivalent of 1,4-dibromo butane-2,3-dione was dissolved

in acetonitrile and stirred for 24 h, the solid that separated was filtered, washed with  $\text{NaHCO}_3$  and recrystallised from DMF/acetonitrile mixture. The physical data of all the synthesized compounds is presented in Table 1.

## RESULTS AND DISCUSSION

Many enzymes exist as dimers in their active form. This may be the reason that the dimerised pharmacophores shows better activity by binding through the appropriate epitopes in a facile manner at the dimeric binding site of the macromolecule. Here we dimerised the pharmacophore showing antiinflammatory activity developed in our laboratory (Tables 2 and 3). Most of the dimeric compounds showed better antiinflammatory activity than their parent monomer type compound. Few compounds like G-6, G-7, G-8, G-12, G-16, G-17, G-18, G-19, G-20 and G-21 gave protection by more than 50%

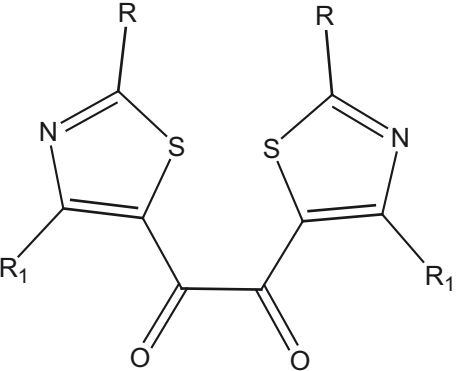
**TABLE 2: ANTIINFLAMMATORY ACTIVITY OF 1,2-BIS[2-(ALKYL/ARYLAMINO)-4-ALKYL/ARYL-1,3-THIAZOL-5-YL]ETHANE-1,2-ONES**



CODE	R	R1	% PROTECTION Dose 100 mg/kg b.w
G-1	$\text{CH}_3$	$\text{CH}_3$	14±7
G-2	$\text{C}_6\text{H}_5$	$\text{CH}_3$	23±8
G-3	p-Cl- $\text{C}_6\text{H}_4$	$\text{CH}_3$	73±0.3
G-4	$\text{CH}_3\text{OCO}$	$\text{CH}_3$	40±2
G-5	$\text{C}_2\text{H}_5\text{OCO}$	$\text{CH}_3$	33±0.9
G-6	$\text{C}_6\text{H}_5\text{CO}$	$\text{C}_6\text{H}_5$	74±0.5
G-7	$\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_5$	70±0.7
G-8	p-Cl- $\text{C}_6\text{H}_4$	$\text{C}_6\text{H}_5$	66±1
G-9	$\text{CH}_3\text{OCO}$	$\text{C}_6\text{H}_5$	26±3
G-10	$\text{C}_2\text{H}_5\text{OCO}$	$\text{C}_6\text{H}_5$	34±4
G-11	$\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_5\text{CH}_2$	23±2
G-12	p-Cl- $\text{C}_6\text{H}_4$	$\text{C}_6\text{H}_5\text{CH}_2$	72±1
G-13	$\text{CH}_3\text{OCO}$	$\text{C}_6\text{H}_5\text{CH}_2$	35±2.5
G-14	$\text{C}_2\text{H}_5\text{OCO}$	$\text{C}_6\text{H}_5\text{CH}_2$	38±2
G-15	$\text{C}_6\text{H}_5\text{CO}$	$\text{C}_6\text{H}_5\text{CH}_2$	47±2.3

\*Ibuprofen was taken as positive control which 65 % inhibition at 100 mg/kg

**TABLE 3: ANTIINFLAMMATORY ACTIVITY OF 1,2-BIS[2-(DIALKYLAMINO)-4-HETERYL-1,3-THIAZOL-5-YL]ETHANE-1,2-ONES**



CODE	R	R1	% PROTECTION
G-16	piperidinyl	$\text{C}_6\text{H}_5$	65±0.8
G-17	4-morpholinyl	$\text{C}_6\text{H}_5$	81±0.5
G-18	N-methylpiperazinyl	$\text{C}_6\text{H}_5$	60±0.5
G-19	N-ethylpiperazinyl	$\text{C}_6\text{H}_5$	72±0.5
G-20	N-phenylpiperazinyl	$\text{C}_6\text{H}_5$	55±4
G-21	N-benzylpiperazinyl	$\text{C}_6\text{H}_5$	85±0.3

**TABLE 4: INHIBITORY POTENCIES AS MEASURED IN AN EXTRACELLULAR HIV-1 INTEGRASE ASSAY**

Compounds	3'P ( $\mu\text{m}$ )	ST ( $\mu\text{m}$ )
G-3	132	397
G-6	>500	277
G-17	>500	109
G-20	122	87
G-23	276	276
G-22	287	>500
L-708,906	>1000	0.48

No other compounds showed any activity in concentration range 500  $\mu\text{m}$

in the carrageenan rat paw model. The compounds with a bulky and lipophilic group at the 2 and 2' position showed excellent antiinflammatory activity. However, representative examples of these classes of compounds did not have any effect on TNF- $\alpha$  release from human peripheral blood mononuclear cells (G-6, G-17, G-19) and one compound weakly inhibited cPLA<sub>2</sub>(G-6).

In the integrase assay few compounds showed weak activity (Table 4). The pharmacophore of the reported compounds contains hetero aryl ring connected by a linker containing diketo functionality. The weak activity of our compounds may be due to the fact that in the reported potent HIV-1 integrase inhibitors, besides the diketo moiety an additional carboxylic acid moiety is present and this feature may also be necessary for good antiintegrase activity. In conclusion the good antiinflammatory activity shown by G3, G6, G7 and G12 seem to indicate the utility of this framework as a lead with a potential to optimize to a developable drug-like candidate to treat inflammatory diseases.

## ACKNOWLEDGEMENTS

The authors acknowledge Prof. Nouri Neamati for screening the compounds in HIV-integrase assay, Prof Mathius Lehr for screening the compounds in cPLA<sub>2</sub> assays and CSIR New Delhi for financial assistance.

## REFERENCES

- Gabriel SE. The epidemiology of Rheumatoid arthritis. *Rheum Dis Clin North Am* 2001;27:269-81.
- Lee DM, Weinblatt ME. Rheumatoid arthritis. *Lancet* 2001;358:903-11.
- Smolen JS, Steiner G. Therapeutic strategies for Rheumatoid arthritis. *Nat Rev Drug Disc* 2003;2:473-80.
- Palladino MA, Bahjat FR, Theodorakis EA, Moldawer LL. Anti-TNF- $\alpha$  therapeutics: The next generation. *Nat Rev Drug Disc* 2003;2:736-41.
- Smolen JS, Kalden JR, Scott DL, Rozman B, KvienTK, Larsen A, *et al.* Efficacy and safety of leflunomide compound with placebo and sulphasalazine in active rheumatoid: A double-blind, randomised, multi centre trial. *Lancet* 1999;353:259-61.
- Pillai AD, Rathod PD, Franklin PX, Padh H, Vasu KK, Sudarsanam V. Design, synthesis, and SAR studies of some 5-aliphatic oximino esters of thiophene as potential anti-inflammatory leads: comparative biological activity profile of aliphatic oximes vs aromatic oximes. *Biochem Biophys Res Com* 2004;317:1067-71.
- Tuma RS. Drug designers seek a structural solution, *Drug Discovery Today* 2003;8:1012-5.
- Neamati N, Lin Z, Karki RG, Orr A, Cowansage K, Strumberg D, *et al.* Metal-Dependent Inhibition of HIV-1 Integrase. *J Med Chem* 2002;45:5661-7.
- Kumar A, Katiyar SB, Agarwal A, Chauhan PM. Current trends in anti-malarial chemotherapy. *Drugs Fut* 2003;28:243-7.
- Johnson TO, Ermolieff J, Jirousek MR. Protein tyrosine phosphatase 1B inhibitors for diabetes. *Nat Rev Drug Disc* 2002;1:696-709.
- Pais GC, Zhang X, Marchand C, Neamati N, Cowansage K, Svarovskaia ES, *et al.* Structure Activity of 3-aryl-1,3-diketo-containing compounds as HIV-1 Integrase Inhibitors. *J Med Chem* 2002;45:3184-94.
- Pommier Y, Johnson AA, Marchand C. Integrase Inhibitors to treat HIV/Aids. *Nat Rev Drug Disc* 2005;4:236-43.
- Rajappa S. A novel synthesis of thiazoles: Synthesis of 2-amino-5-nitrothiazoles by direct ring closure reactions, *Indian J Chem B* 1978;16:745-8.
- Rajappa S, Advani BG. A novel synthesis of thiazoles. *Indian J Chem* 1970;8:1145-8.
- Rajappa S, Nair MD, Advani BG, Sreenivasan R, Desai JA. A general synthesis of thiazoles. Part 3: Comparative evaluation of different functionalised thioureas as precursors. *J Chem Soc Perkin Trans I* 1979;1762-4.
- Rajappa S. A general synthesis of thiazoles: Part-4: Synthesis of 5-acyl-2,4-diaminothiazoles Proceedings of Indian Academy of Sciences. *Chem Sci* 1982;9:441-4.
- Rajappa S. A general synthesis of thiazoles: Part-6: Synthesis of 2-amino-5-heteryl thiazoles. Proceedings of Indian Academy of Sciences. *Chem Sci* 1982;9:1:451-5.
- Hodgkins JE, Reeves WP. The modified kaluza synthesis III: The synthesis of some aromatic isothiocyanates. *J Org Chem* 1964;29:3098-9.
- Esmail R. The chemistry of ethoxycarbonyl isothiocyanates and related compounds. *Synthesis* 1975;301:314-7.
- Reeves WP, Simmons Jr A, Rudis JA, Bothwell TC. Phase transfer catalysis preparation of acyl isothiocyanates. *Synthetic Comm* 1981;11:781-5.
- Franklin PX. Design, synthesis and pharmacological evaluation of novel five membered heterocyclic derivatives as potential therapeutic agents Ph.D thesis submitted to Bhavnagar University. September 2004.
- Marchand C, Neamati N, Pommier Y. *In vitro* human immunodeficiency virus type 1 integrase assays. *Met Enzymol* 2001;340:624-7.
- Pillai AD, Rathod PD, Franklin PX, Patel M, Nivsarkar M, Vasu KK, *et al.* Novel drug designing approach for dual inhibitors as anti-inflammatory agents: Implication of pyridine template. *Biochem Biophys Res Comm* 2003;301:183-7.
- Ruggli P, Herzog M, Wegmann J, Dahn H. Carbonyl groups and aromatic hydrocarbons: Addition of benzene to symmetrical dibromobiacetyl. *Helv Chim Acta* 1946;29:95-101.

Accepted 17 May 2009

Revised 6 April 2009

Received 14 June 2006

Indian J. Pharm. Sci., 2009, 71 (3): 259-263