Selective Synthesis of 3-(α,α-Dibromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one as an Excellent Precursor for the Synthesis of 2-Substituted 4-(4-Hydroxy-6-methyl-2*H*-2-oxopyran-3-yl)thiazoles as Antimicrobial and Antifungal Agents

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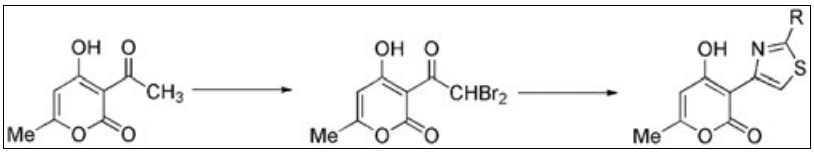

A selective synthesis of 3-(α,α-dibromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**) has been achieved by bromination of DHA using $CuBr_2$/$CHCl_3$-EtOAc. The reaction of **3** with different thioureas/thiomides/thiosemicarbazide offers a convenient and efficient method for the syntheses of 2-substituted 4-(4-hydroxy-6-methyl-2*H*-2-oxopyran-3-yl)thiazoles. These thiazoles were evaluated for their antimicrobial and antifungal activity.

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INTRODUCTION

2-Pyrone and coumarin derivatives constitute an exceptional class of heterocyclic compounds. They are useful precursors for various compounds having diverse biological properties, abundantly found in animals, insects, plants, bacteria, and microbial systems [1–7]. They play a key role in medicinal area and can be obtained by making small changes in the substitution pattern on the 2-pyrone ring. For instance, 4-hydroxy-2-pyrones are not only considered as one of important classes of anti-HIV agents but also exhibit a wide range of antifungal, phytotoxic, antimicrobial, cytotoxic, and neurotoxic activities [8–10]. Another significant property found in 2-pyrone derivatives is their potential in the treatment of Alzheimer's and other dementia diseases [11,12]. The most important and widely studied 4-hydroxy-2-pyrone derivative is 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (**l**, dehydro acetic acid, abbreviated as DHA). This pyrone derivative has been isolated from natural sources [13,14] and is also industrially available utilizing a number of synthetic procedures [15–18]. The reactions of DHA and its derivatives have shown wide utility in organic syntheses including various heterocyclic compounds [19–21]. DHA is converted into 4-hydroxy-6-methyl-2*H*-pyran-2-one 2 (triacetic lactone) by the action sulfuric acid [8]. These two natural occurring 2-pyrones have been extensively studied as building blocks for a wide range of important biologically active heterocyclic compounds, such as pyrimidines, pyridines, thiadiazoles, pyrazoles, bipyrazoles, pyranopyrans, and benzodiazepines [22–27].

The DHA molecule can exist in several tautomeric forms, and structures of two important tautomers are shown as **1** and **la** (Chart 1). Since DHA has several reactive sites, the molecule is susceptible to the attack by the nucleophilic and electrophilic reagents. A nucleophile can, in principle, attack the carbonyl of C(3)-acetyl the carbon atom terminating the conjugated carbon chain 6-position the lactone carbonyl at 2-position and the carbon at position 4. On the other hand, an electrophile can attack at positions 3,5,α-position of acetyl group, and oxygen of C(4)-OH.

Because of availability of several reactive sites for nucleophilic and elecrophilic attack, problems of selectivity are generally encountered in the reactions of DHA. For example, bromination of DHA gives different brominated products depending upon the nature of reagent and conditions [28–32] employed in the reaction. The reported results are summarized in Chart 2.

In continuation of our interest in the use of DHA and its derivatives as a versatile precursors for the synthesis of various heterocyclic compounds, we became interested in the synthesis of 2-substituted 4-(4-hydroxy-6-methyl-2*H*-2-oxopyran-3-yl)thiazoles starting from DHA. In a recent study by Hikam-Oukacha *et al*., [31] it has been reported that such thiazoles can be synthesized by the reaction of 3-(α-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (**2**) with thioamides and related compounds (Hantzsch thiazole synthesis, [33], Method I). In this report, the authors have also addressed the problem related to reproducibility of the results on bromination of DHA using bromine under various conditions. They prepared

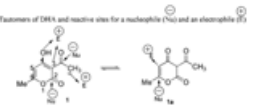


Chart 1. Tautomers of DHA and reactive sites for a nucleophile $\overset{\ominus}{(Nu)}$ and an electrophile $\overset{\oplus}{(E)}$

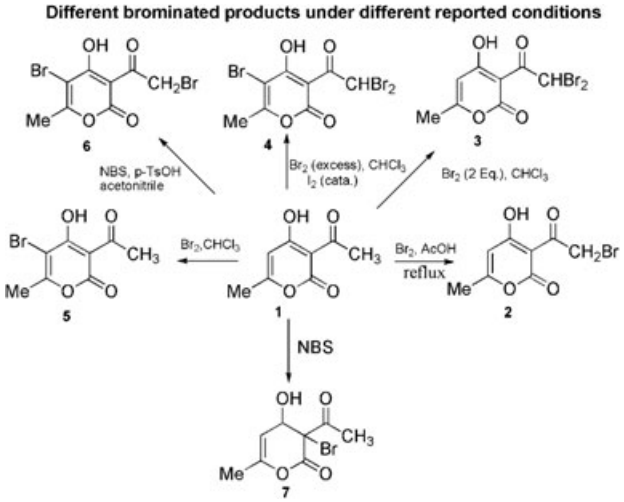
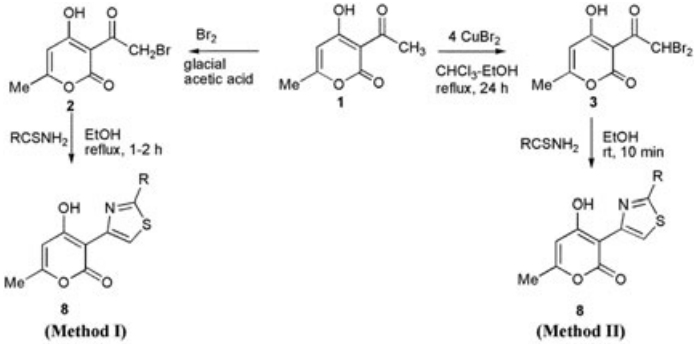


Chart 2. Different brominated products under different reported conditions

α-bromoketone **2** in 61% yield by using bromine in acetic acid under refluxing conditions [31].

Despite the fact that Hikam-Oukacha *et al*. [31] succeeded in the selective bromination of DHA into **2** and then synthesis of thiazoles **8** by Method I, there has been great demand to develop some alternative approaches for such syntheses avoiding the use molecular bromine and α-bromoketones [34] because of several practical problems associated with them. In this context, we and other research groups have earlier shown that α,α-dibromketones behave analogous to α-bromoketones in their reactions with certain nulceophiles such as sulfur nucleophile and bidentate nucleophiles containing nitrogen and sulfur atoms [35–44]. These studies involving α,α-dibromoketones have offered a valuable modification to the most widely used Hantzsch thiazoles synthesis [33]. Prompted by previous work on the use of α,α-DBKs, we herein wish to report our results on the selective synthesis of 3-(α,α-dibromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**) by using $CuBr_2/CHCl_3$-EtOAc [45] and its use as a precursor in developing an efficient and convenient synthesis of 2-substituted 4-(4-hydroxy-6-methyl-2*H*-2-oxopyran-3-yl) thiazole (**8**).

Scheme 1



R= NHC_6H_4-OMe-*p*, dimethylpyrazolyl, $-C_6H_5$, $-NHNH_2$, $-NHC_6H_4NO_2$-*p*, $-NHC_6H_4$-Me-*p*, $-NHC_6H_4$-Cl-*p*, $-NHC_6H_5$

Table 1

Physical data of pyranylthiazoles.

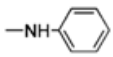
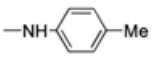
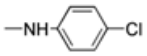
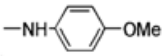
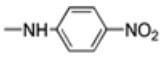
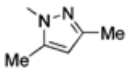
Sr. No	Compound	R	mp (°C)	Yield
1	**8a**		240	90
2	**8b**		235	70
3	**8c**		250	66
4	**8d**		220	74
5	**8e**		200	67
6	**8f**		148	70
7	**8g**		240	60
8	**8h**	$-NHNH_2$	210	72

Table 2

x, *y*, *z* coordinates of grid box (PDB ID: 4EMV).

center_x	23.045
center_y	32.231
center_z	0.769
size_x	40
size_y	40
size_z	40

RESULTS AND DISCUSSION

Chemistry. ***Selective bromination of DHA with $CuBr_2$/$CHCl_3$-EtOAc.*** First, we focused our attention to develop a new method eliminating the use of bromine for the synthesis of α,α-dibromoketone **3**. To the best of our knowledge, among the various reagents, which avoid the use of bromine and have been used for selective bromination of other ketones. Only one reagent system, that is, NBS in combination with *p*-TsOH under various conditions has been reported for selective α-monobromination and α,α-dibromination of DHA [32]. Based on our recent success on selective dibromination of electron-rich ketones such as *o*/*p*-hydroxyacetophenones by the method of King and Ostrum [45] involving heterogeneous reagent system $CuBr_2$/$CHCl_3$-EtOAc, we attempted bromination of DHA by this method.

Interestingly, after some experimentation with changing reaction time and reagent, and monitoring the reaction progress by scanning the ^{1}H NMR of crude product at different intervals, it was found that this method is most suitable for effecting selective α,α-dibromination of DHA. The desired bromoketone was available in high yield without making the use of column chromatography for purification.

The structure of compound **3** was confirmed by the comparison of mps and spectral data (^{1}H NMR and ^{13}C NMR) with those reported in literature. In particular, ^{1}H NMR data were found to be most suitable for monitoring the progress of reaction and identification of the product. The most characteristic feature in the NMR of **3** was appearance of singlets at δ 6.81 due to methine ($CHBr_2$) protons, respectively. The methyl protons (at δ 2.7) of acetyl group of DHA completely disappeared on the formation of the brominated product.

The results of the present study using $CuBr_2$/$CHCl_3$-EtOAc offer a new method for selective high yield α,α-dibromination of DHA [46]. The method is superior to

Scheme 2

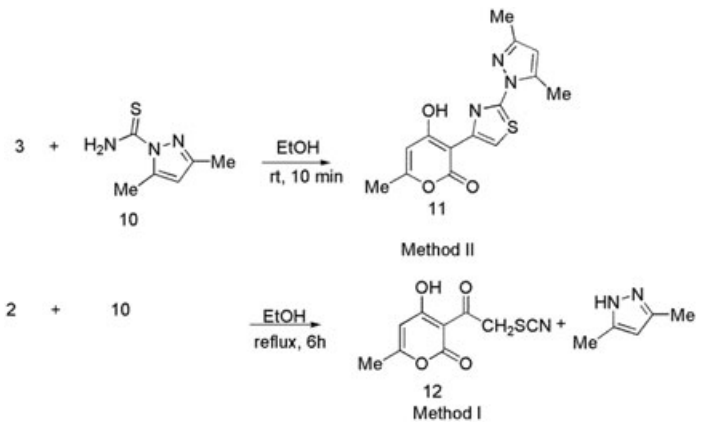


Table 3

pMIC (μmol/mL) values of all the compounds and standard drugs against bacterial and fungal strains.

	Bacterial strains (pMIC μmol/mL)						
	Gram positive			Gram negative		Fungal strains (pMIC μmol/mL)	
Compound	*Staphylococcus aureus*	*Bacillus subtilis*	*Staphylococcus epidermidis*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*	*Aspergillus niger*
8a	1.38	1.38	1.38	1.38	1.38	1.982	1.982
8b	1.4	1.4	1.4	1.4	1.4	2.002	1.099
8c	1.427	1.728	1.427	1.427	1.427	2.029	1.427
8d	1.422	1.422	1.422	1.422	1.422	1.723	1.422
8e	1.441	2.043	1.441	1.441	1.441	2.043	2.043
8f	1.357	1.357	1.357	1.357	1.357	1.658	1.357
8g	1.342	1.342	1.342	1.342	1.342	1.643	1.342
8h	1.281	1.281	1.281	1.281	1.281	1.582	1.281
Ciprofloxacin	3.042	3.042	3.042	3.042	3.042	—	—
Ofloxacin	3.080	3.080	3.080	3.080	3.080	—	—
Fluconazole	—	—	—	—	—	3.008	3.008

Table 4

Binding affinity and binding mode of ligands with receptor (PDB ID: 4EMV).

Compound	Dock score	Number of hydrogen bonds	Amino acids involved in H-bonding	Distance (A°)
8a	−6.8	—	—	—
8b	−7.1	1	THR100	3.107
8c	−7.2	1	THR100	2.984
8d	−7.2	1	THR100	2.112
8e	−7.6	1	LYS154	2.233
8f	−6.8	—	—	—
8g	−6.3	—	—	—
8h	−5.7	1	SER 58	2.093
Ciprofloxacin	−6.3	1	LYS154	1.982
Fluconazole	−6.1	2	SER58	2.017
			ARG81	2.079

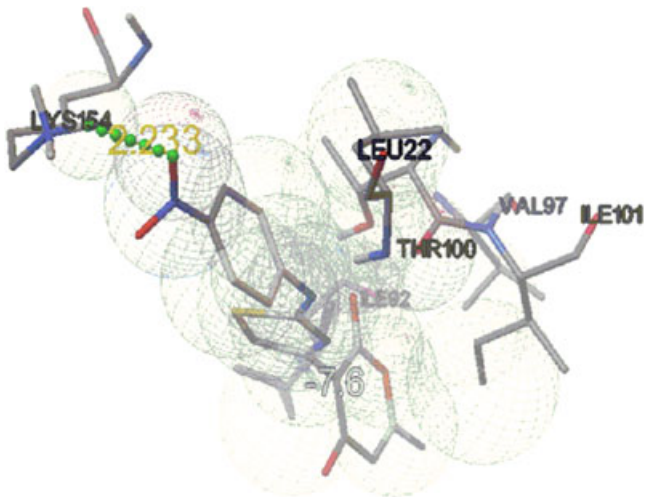


Figure 1. Docking interaction of compound **8e** with microbial receptor (PDB ID: 4EMV) showing hydrogen bond in green line. [Color figure can be viewed at wileyonlinelibrary.com]

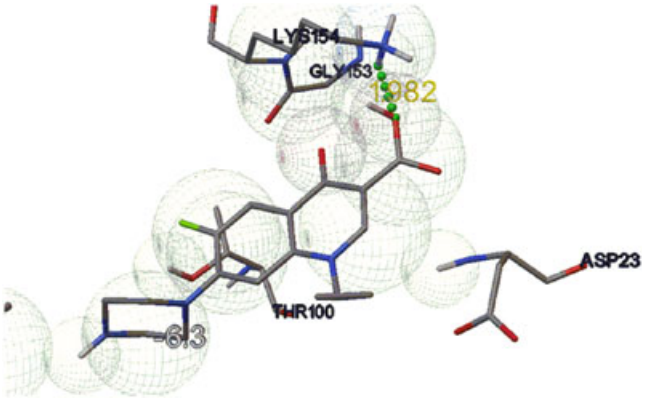


Figure 2. Docking interaction of ciprofloxacin with microbial receptor (PDB ID: 4EMV) showing hydrogen bond in green line. [Color figure can be viewed at wileyonlinelibrary.com]

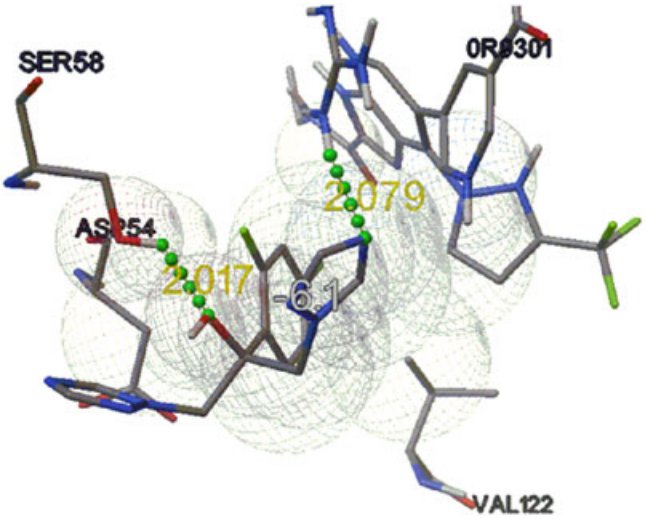


Figure 3. Docking interaction of fluconazole with microbial receptor (PDB ID: 4EMV) showing hydrogen bond in green line. [Color figure can be viewed at wileyonlinelibrary.com]

the reported methods for bromination of ketones in terms of selectivity of the reaction, operational simplicity of the procedure involved, avoiding the use of bromine and dry conditions.

Synthesis of 2-substituted 4-(4-hydroxy-6-methyl-2H-2-oxopyran-3-yl)thiazoles (8) (Method II). As mentioned earlier, DBKs can offer a superior altenative to the highly lachrymatory BKs, which are extremely useful precursors in the Hantzsch reaction for thiazoles synthesis. The DBks-based Hantzsch modification has also provided an efficient synthesis of bromopyranylthiazoles [27,28]. Delighted by this observation, we investigated the reactivity of 3-(α,α-dibromoacetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**) toward some thioamides, thioureas, thiosemicarbazide, and thiosemicarbazoes with the hope of obtaining the corresponding 2-substituted pyranylthiazoles. Initially, we attempted the reaction of **3** with *N*-phenylthiourea in ethanol by stirring the equimolar mixture of the reactants at room temperature. The reaction occurred according to the expectation with the formation of **8a** as a yellow solid within 5–10 min. This was an encouraging observation as the desired product was isolated simply by filtration in ~90% yield and almost in pure state without further purification. The other nucleophilic reactants also reacted with **3** in a similar manner to afford the desired thiazoles in high yields (Scheme 1, Table 1).

A comparison of our results (Method II) with the recently reported compounds involving α-bromoketone **2** (Method I) clearly indicates that Method II is superior in terms of operational simplicity, yields, time, and temperature required for reaction. While studying the scope of present study on the new examples, it was found that the reaction of 3′5-dimethylpyrazole-1-thiocarboxamide is particularly noteworthy. In this case the reaction with **3** (Method II)

occurred smoothly at room temperature with the formation of desired thiazole derivative **8**, whereas the reaction with **2** (Method I) gave a mixture of 3,5-dimethylpyrazole and α-thiocyanatoketone rather than the expected thiazole **8**. The harsh reaction condition (refluxing for long time), involved in Method I probably led to decomposition of thiocarboxamide with the generation of 3,5-dimethylpyrazole and α-thiocyanatoketone, formed by the nucleophilic substitution of **2** with insitu-generated thiocyanate (Scheme 2). Obviously, the present method involving dibromoketone with milder conditions is of wider application. The thiazole derivatives synthesized in this work may find applications as biologically active compounds.

CONCLUSIONS

In summary, we report herein selectively synthesized 3-(α,α-dibromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**) using $CuBr_2/CHCl_3$-EtOAc. This study provides the cleanest method for preparation of **3**, which is an excellent precursor for the synthesis of 2-substituted 4-(4-hydroxy-6-methyl-2*H*-2-oxopyran-3-yl)thiazoles of great biological importance.

Biological screening. ***Antimicrobial activity.*** The synthesized compounds were evaluated for their in vitro antimicrobial activity against bacterial (both Gram positive and Gram negative) and fungal strains by using serial dilution technique to find their minimum inhibitory concentration [47]. The nutrient media were prepared by dissolving weighed amount of nutrient broth and sabouraud dextrose broth in distilled water for bacteria and fungus respectively and 1 mL of nutrient medium will be transferred to each test tube; 0.01 g of synthesized drug sample was dissolved in 10 mL of dry DMSO to give a stock solution of 100 μg/mL. The solution of test compounds was transferred to test tubes having sterilized nutrient medium to obtain a set of five dilutions of test compounds having concentrations 50, 25, 12.5, 6.25, and 3.125 μg/mL. Minimal inhibitory concentration for each sample was investigated against three Gram-positive bacterial strains, *Staphylococcus aureus* (MTCC 7443), *Bacillus subtilis* (MTCC 441), and *Staphylococcus epidermidis* (MTCC 6880); against two Gram-negative bacterial strains, *Pseudomonas aeruginosa* (MTCC 424) and *Escherichia coli* (MTCC 1652); and two fungal strains, *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 8189). The freshly cultured strains of each organism were transferred into test tubes and incubated at 37 ± 1°C for 24 h for bacterial strains, 48 h for *C. albicans* and 7 days at 25 ± 1°C for *A. niger* [48]. Ciprofloxacin and ofloxacin were considered as reference standard for antibacterial activity and fluconazole for antifungal activity. The minimum concentration of each compound that prevented visible growth of microbes was considered as minimal inhibitory concentration.

Docking studies. The molecular docking study of the series was performed using AutoDockVina program [49], and the 2D structure of all the ligand molecules was prepared in MarvinSketch 6.2.2 (ChemAxon, Budapest, Hungary) and then converted into 3D for energy minimization and saved in pdbqt format using AutoDock Tools 1.5.6. The crystal structure of 4EMV was retrieved from protein data bank (www.rcsb.org) for docking simulations [50]. As protein preparation, the water of crystallization was removed and polar hydrogens were added. In AutoDockVina, the active binding cavity was generated as grid box with specific parameters given in Table 2. Docked structures were visualized using PyMOL, and the results were analyzed to obtain familiar with the interaction of ligand molecules with receptor [51].

Antimicrobial activity. The synthesized compounds were evaluated for their in vitro antibacterial activity against pathogenic strains including Gram-positive bacteria (*S. aureus*, *B. subtilis,* and *S. epidermidis*) and Gram-negative bacterial strains (*P. aeruginosa* and *E. coli*). The compounds were also screened against fungal strains, *C. albicans* and *A. niger*. pMIC calculated from MIC was considered for the evaluation of antimicrobial study, and values for each compound and standard drugs as well have been provided in Table 3 against all strains of bacteria and fungus.

Compound **8e** displayed maximum value of pMIC against all the strains of microorganisms and found to be most potent compound among the series. It is clearly indicated that the presence of electron-withdrawing group ($-NO_2$) led to the development of most active scaffold. Compound **8c**, halogen substituted, was also found to be almost equally potent against bacterial strain. Compound **8h** was found to be least active among the series and revealed that the absence of aromatic ring next to thiazole ring decreased the activity.

One more interesting finding displayed by **8a** is unsubstituted aromatic ring that the compound was not possessing activity against any strain of bacterial while having good potency against fungal strain. This might help us to synthesize drugs having specific action against fungal infection. The interaction of compounds with the receptor molecule is further studied with the help of molecular docking.

Docking study. In the docking study, all the synthesized compounds were docked into the cavity of receptor (PDB ID: 4EMV) using AutoDockVina. The present molecular docking study provided a significant insight into ligand-receptor binding as well as binding mode. The binding energy and pattern of the ligands with protein is provided

in Table 4. The result clearly indicated that the compound **8e** should possess the maximum potency against microbes as the binding energy was calculated as −7.6 kcal/mol, best dock score among the series. The interacting residues notable for binding are THR100, SER58, LYS154, and ARG81. The interaction of compound **8e**, ciprofloxacin, and fluconazole via hydrogen bonding has been shown in Figures 1–3, respectively.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker 400 MHz instrument using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer 1800 IR spectrophotometer. Most of the common chemicals such as dehydroacetic acid, bromine, and $CuBr_2$ were obtained from commercial suppliers.

3-(α,α-Dibromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (3). The copper(II) bromide was finely ground, without drying, in a mortar and pestle to ensure large surface area for reaction. Copper(II) bromide (0.05 mole) was placed in a conical flask fitted with a reflux condenser, and ethyl acetate (25 mL) was added. To the resulting suspension was added the solution of DHA (1, 0.03 mole) in hot chloroform (25 mL). The reaction mixture was refluxed with vigorous stirring until the reaction was complete within 10 h, as judged by color change of the solution from green to amber, disappearance of all black solid, and cessation of hydrogen bromide evolution and TLC of the crude product. The reaction mixture was allowed to cool to room temperature, and thus, the resulted solid Cu(I)Br was removed by filtration. The filtrate was washed with aqueous sodium metabisulphite solution, and solvents were removed from the filtrate under reduced pressure to give the desired α,α-dibromo DHA (**3**).

mp 88–89°C (lit mp 88–89°C; yield 85%), IR (ν_{max}, cm^{-1}, KBr): 3400, 1730, 1630, 1570, 1H NMR($CDCI_3$, δ): 2.4 (s, 3H), 7.4(s, 1H), 6.04 (s, 1H).

General procedure for the synthesis of 2-substituted 4-(4-hydroxy-6-methyl-2*H*-2-oxopyran-3-yl)thiazoles. To the solution of (2 mmol, **3**) in ethanol (10 mL) was added thioamide or thiourea or thiosemicarbazone (2 mmol), and the mixture (solution or suspension) was allowed to stir at room temperature. After about 10 min, a solid separated out, which was recrystallized from ethanol. Spectral and analytical data of the products are as follows.

4-(4-Hydroxy-6-methyl-2-pyran-3-yl)-2-aminophenylthiazole (8a). Yellow solid. IR (ν_{max}, cm^{-1}, KBr): 3100–3500 cm^{-1}, 1703 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 2.44(s, 3H, ─CH_3), 7.34–7.50 (m, 5H, Ar), 6.2 (s, 1H, pyrone), 7.2 (s, 1H, thiazole). ^{13}C NMR (DMSO-d_6): 19.4 (─CH_3), 24.3 (3 ─CH_3), 101.1(thiazole), 101.9 (aromatic ring), 159 (thiazole), 160 (carbonyl, C═O).

4-(4-Hydroxy-6-methyl-2-pyran-3-yl)-2-amino-(-4′-methyl) phenylthiazole (8b). Yellow solid. IR (ν_{max}, cm^{-1}, KBr): 3100–3500 cm^{-1}, 1704 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 1.98 (s, 3H, CH_3), 2.35(s, 3H, ─CH_3), 7.0–7.5(m, 4H), 6.2 (s, 1H, pyrone), 5.5 (s, 1H, thiazole). ^{13}C NMR (DMSO-d_6): 19.4 (3 ─CH_3), 24.3 (3 ─CH_3), 101.1(thiazole), 101.9 (aromatic ring), 159 (thiazole), 160 (carbonyl, C═O). MS (ES+): m/z M^+ (315).

4-(4-Hydroxy-6-methyl-2-pyran-3-yl)-2-amino-(-4′-chloro) phenylthiazole (8c). Yellow solid. IR (ν_{max}, cm^{-1}, KBr): 3100–3500 cm^{-1}, 1701 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 2.4(s, 3H, ─CH_3), 7.34–7.50 (m, 4H), 6.2 (s, 1H, pyrone), 6.4 (s, 1H, thiazole). ^{13}C NMR (DMSO-d_6): 19.4 (─CH_3), 24.3 (3 ─CH_3), 101.1(thiazole), 101.9 (aromatic ring), 159 (thiazole), 160 (carbonyl, C═O). MS (ES+): m/z M^+ (335), M^+ +2 (337).

4-(4-Hydroxy-6-methyl-2-pyran-3-yl)-2-amino-(-4′-methoxy) phenylthiazole (8d). Yellow solid. IR (ν_{max}, cm^{-1}, KBr): 1704 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 2.30 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 7.24–7.38 (m, 4H, Ar), 6.2 (s, 1H, pyrone), 7.4(s, 1H, thiazole). ^{13}C NMR (DMSO-d_6): 20 (3 ─CH_3), 55(3C, OCH_3), 101.1(thiazole), 101.9 (aromatic ring), 168(C═O).

4-(4-Hydroxy-6-methyl-2-pyran-3-yl)-2-amino-(-4′-nitro) phenylthiazole (8e). Yellow solid. IR (ν_{max}, cm^{-1}, KBr): 3100–3500 cm^{-1}, 1700 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 2.39 (s, 3H, CH_3), 7.5–8.5(m, 4H), 6.2 (s, 1H, pyrone), 5.5 (s, 1H, thiazole).

^{13}C NMR (DMSO-d_6): 19.4 (3 ─CH_3), 101.1(thiazole), 101.9 (aromatic ring), 143 (thiazole), 168 (carbonyl, C═O).

4-(4-Hydroxy-6-methyl-2-pyran-3-yl)-2-phenylthiazole (8f). Yellow solid. IR (ν_{max}, cm^{-1}, KBr): 3100–3500 cm^{-1}, 1703 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 2.50 (s, 3H, CH_3), 7.49–7.91 (m, 5H, Ar), 6.2 (s, 1H, pyrone), 7.4(s, 1H, thiazole). ^{13}C NMR (DMSO-d_6): 21 (3 ─CH_3), 101.1(thiazole), 101.9 (aromatic ring), 168(C═O).

4-(4-Hydroxy-6-methyl-2-pyran-3-yl)-2-(3,4-dimethylpyrazolylthiazole (8g). Dark yellow solid. IR (ν_{max}, cm^{-1}, KBr): 3100–3500 cm^{-1}, 1700 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 2.40 (s, 3H, CH_3), 2.79 (s, 3H, ─CH_3), 2.05 (s, 3H, ─CH_3), 4.99 (s, 2H, ─CH_2), 6.2 (s, 1H, pyrone), 7.1(s, 1H, thiazole), 7.23 (1H pyrazole). ^{13}C NMR (DMSO-d_6): 20 (3 ─CH_3), 55(3C, OCH_3), 101.1(thiazole), 101.9 (aromatic ring), 134(pyrazol), 143 (thiazole), 168 (carbonyl, C═O).

4-(4-Hydroxy-6-methyl-2-pyran-3-yl)-2-hydrazinylthiazole (8h). Yellow solid. IR (ν_{max}, cm^{-1}, KBr): 3100–3500 cm^{-1}, 1754 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 2.23 (s, 3H, CH_3), 6.2 (s, 1H, pyrone), 7.43(s, 1H, thiazole). ^{13}C NMR (DMSO-d_6): 19.4 (3 ─CH_3), 101.1(thiazole), 101.9 (aromatic ring), 143 (thiazole), 168 (carbonyl, C═O).

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