RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

One pot synthesis of tetrasubstituted thiophenes: [3+2] Annulation Strategy

Satya Narayan Sahu,[a] Maneesh Kumar Gupta,[a] Surjeet Singh,[a] Pratik Yadav,[a] Rahul Panwar,[a] Abhinav Kumar,[b] Vishnu Ji Ram,[b] Brejesh Kumar[c] and Ramendra Pratap[a,*]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A simple, efficient and economical synthesis of dimethyl 3-amino-5-(2-oxo-2-arylethyl)thiophene-2,4-dicarboxylates has been reported by ring opening of methyl 3-amino-6-aryl-4-oxo-4*H*-thieno[3,2-*c*]pyran-2-carboxylates by alkoxide ion. Pyranothiophenes have been obtained by the reaction of methyl thioglycolate and 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles in the presence of triethyl amine. One-pot multicomponent protocol for the synthesis of tetrasubstituted thiophenes has been developed by reaction of 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles and methyl thioglycolate in the presence of sodium methoxide in excellent yields. The structure of the isolated compound was confirmed by single crystal X-ray diffraction and spectroscopic studies.

Thiophene is one of the important class of heterocyclic scaffolds of biological importance, widely present in various natural products[1] and therapeutics as substructure. These are very useful as allosteric agonists and modulators of the adenosine A1 receptor 2A3BTs[2] and PD81,723[3] (Figure 1). Besides, they are useful as potent PI3K inhibitors[4] and check point kinase inhibitors.[5] Articaine,[6] a thiophene derivative is commonly used

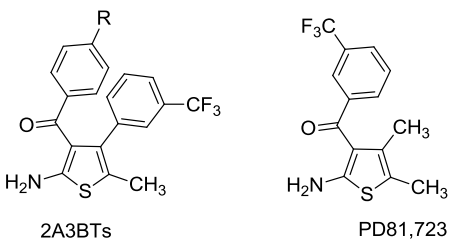


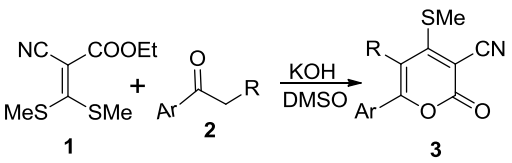
Figure 1: Biologically active thiophenes

as an anesthetic in dental surgery and also PaTrin-2 inhibitor of the DNA repair enzyme, O6-methylguanine-DNA methyl transferase.[7] Recently, numerous thiophene derivatives are reported to display significant activity towards CB1 receptors with good CB1/CB2 selectivity.[8] Additionally, thiophene scaffolds have wide applications as anthelmintics,[9] antiviral,[10] antitumor,[11] anti-inflammatory,[12] antimicrobials,[13] and antiplatelet[14] agents. Further, various thiophene derivatives have broad applications as functional materials in electrically conducting organic materials,[15] semiconductors, [16] light emitting diodes (OLEDs),[17] organic field effect transistors (OFETs),[18] organic solar cells,[19] laser,[20] liquid crystals and molecular wires.[21] The conventional synthetic approaches for the construction of polysubstituted thiophene scaffold include the Gewald,[22] Paal-Knorr,[23] and Fiesselmann[24] syntheses. There is also one report for the construction of tetrasubstituted thiophenes from the reaction of aroyl isothiocyanates with ethyl bromopyruvate in the presence of enaminone in good to excellent yields.[25] El-Saghier *et al.*[26] have reported numerous highly functionalized thiophene scaffolds via ketene S,S- and S,N-acetals.[27] Recently, a novel approach to the synthesis of tetrasubstituted thiophenes is reported in two steps from *trans*-2-aroyl-arylcyclopropane-1,1-dicarboxylates and 1,4-dithianes-2,5-diol.[28] Amongst various approaches, modification of pre-existed thiophene ring system through α-metalation or β-halogenation also provided an alternative route to deliver highly functionalized thiophenes.[29] A regioselective synthesis of polysubstituted thiophenes from Baylis-Hillman adducts has been reported by Kim and coworkers.[30] Further, development in the synthetic methodology opened a new avenue for the construction of trisubstitutedthiophenes by reacting β-ketothioesters with dialkyl acetylenedicarboxylates.[31] Recently, thiophenes are prepared by annulation of β-ketothioamides with arylglyoxal and 5,5-dimethyl-1,3-cyclohexanedione in CF_3CH_2OH.[32] Ram et al.[33] have also reported an elegant approach to the synthesis of trisubstitutedthiophenes through ring transformation of suitably functionalized 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles[34] by alkyl thioglycolate in the presence of NaOH in methanol under reflux condition. Although the existing procedures are very useful for the construction of various thiophene derivatives but most of them suffer with certain limitations of harsh reaction conditions, use of expensive catalysts, long reaction time, multistep approach, use of strong base, difficulty in purification and compatibility of functional groups towards reagents under applied reaction conditions. Therefore, search for highly efficient and economical route was inevitable in view of their wide-ranging applications in the field of material science and pharmaceuticals.

Our quest to develop an efficient and economical protocol for the construction of tetrasubstituted thiophenes did not diminish by using 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles (**3**)[34] as

precursors, obtainable from the reaction of ethyl 3,3-dimethylthio-2-cyanoacrylate (**1**) and aryl methyl or aryl aralkyl ketones (**2**) separately, Scheme 1.

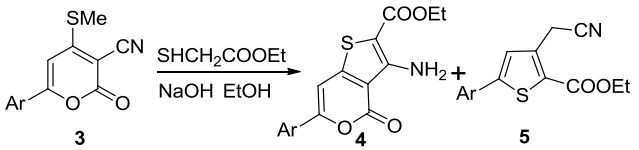
Scheme 1: Synthesis of 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles (**3**)



From the structural dissection, **3** may be considered as a cyclic ketenehemithioacetal and can be exploited for the construction of thiophene scaffolds. Thus, the reaction of **3** with ethyl thioglycolate in the presence of NaOH in methanol at reflux temperature delivered a mixture of ethyl 3-amino-6-arylthieno[3,2-*c*]pyran-4-one-2-carboxylates (**4**) as major product and trisustitutedthiophene, ethyl 5-aryl-3-cyanomethyl-2-carboxylates (**5**) in 30-60% yields, Scheme 2.

Therefore, we planned an entirely new synthetic strategy through ring transformation of **3** by oxazolidene-2,4-dione in the presence of CH_3ONa under reflux condition. This reaction after usual workup delivered a complex mixture. However, we succeeded to isolate a compound in poor yield, which was characterized as methyl 3-amino-5-(2-oxo-2-arylethyl)thiophene-2,4-dicarboxylate by X-ray diffraction and spectroscopic studies. A plausible mechanism of this reaction is depicted in Scheme 3. The ring opening of lactone (**3)** in alkoxide provides methyl 2-

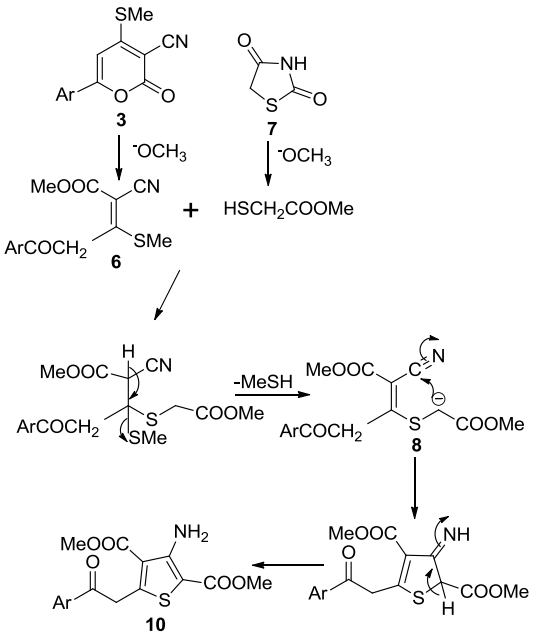
Scheme 2. Synthesis of ethyl 3-amino-6-arylthieno[3,2-*c*]pyran-4-one-2-carboxylates (**4**) and ethyl 6-aryl-3-cyanomethylthiophen-2-carboxylates (**5**)



cyano-3-methylthio-3-aroylmethylacrylate (**6**), while thiozolidenedione under analogous reaction conditions is reported[35] to give methyl thioglycolate *in situ*. Both the reactants **6** and methyl thioglycolate generated in situ from thiozolidenedione react under basic conditions at reflux temperatureto afford polyfunctionalized thiophene **10**. The first step in the formation of tetrasubstitutedthiophene (**10**) is the ring opening of lactone **3** and thiazolidinedione (**7**) in the presence of CH_3ONa to give **6** and methyl thioglycolate, which underwent Michael addition followed by elimination of methyl mercaptan to afford intermediate **8**, which on recyclization produced tetrasubstitutedthiophene (**10**), Scheme 3.

Albeit, we succeeded to synthesize tetrasubstitutedthiophenes (**10)** in single step but the yield was poor. From careful topographical analysis of **4**, we envisaged that alkoxide mediated ring opening of methyl 3-amino-6-arylthieno[3,2-*c*]pyran-4-one-2- carboxylates (**4**)[33,36] may deliver the desired thiophene in high

Scheme 3: A plausible mechanism for the formation of tetrasubstituted-thiophene (**10**)



yield. Therefore, methyl 3-amino-6-arylthieno[3,2-*c*]pyran-4-one-2-carboxylates (**4)** was stirred in freshly prepared solution of

Scheme 4: Synthesis of tetrasubstituted thiophenes **10**

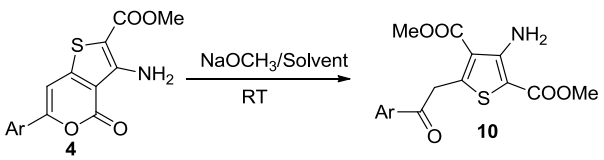


Table 1. Synthesis of tetrasubstituted thiophenes (**10**)[a]

10	Ar	Yield (%) (in Methanol)	(in DMF)
a	C_6H_5	76[c]	90[b]
b	*p*-$CH_3.C_6H_4$	68[c]	88[b]
c	*p*-F.C_6H_4	71[c]	80[b]
d	*p*-Cl.C_6H_4	65[c]	71[b]
e	*o*- Cl.C_6H_4	70[c]	71[b]
f	*p*-Br.C_6H_4	60[c]	70[b]
g	*m*-Br. C_6H_4	50[c]	65[b]
h	2-naphthyl	65[c]	87[b]
i	1-naphthyl	68[c]	84[b]
j	*p*-$OCH_3.C_6H_4$	65[c]	78[b]
k	*3,4*-$(OMe)_2.C_6H_3$	70[c]	80[b]
l	*o*-OMe.C_6H_4	65[c]	80[b]
m	2-Theinyl	65[c]	77[b]
n	2-Furyl	80[c]	83[b]
o	*p*-$NO_2.C_6H_4$	78[b]	60[c]

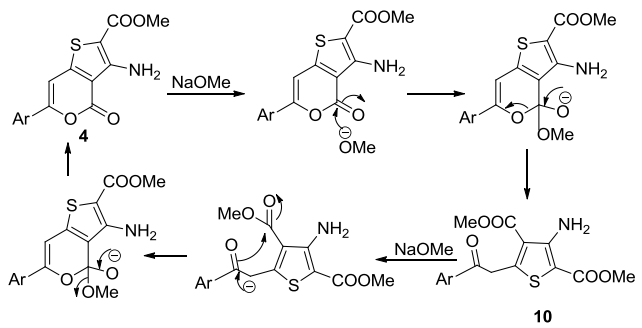
(*a*) All the reaction were carried out by using **4** (0.5 mmol) and sodium methoxide (1.0 mmol) in a solvent (4 ml) at room temperature.(*b*) Yields are reported without further purification through column chromatography.(*c*) Yield are reported after purification through column chromatography.

CH_3ONa in methanol for 1-2 h at room temperature, which produced ring opened compound, similar in all respect to **10**. It

was conspicuous that long duration of stirring provides conversion of **10** to parent compound **4**. Therefore, it was important to monitor the reaction time critically for better yield of **10** (50-80 %). For improving the yields of desired product, we modified the reaction conditions using triethylamine in methanol for the ring opening of **4** at 90° C, but net result was fiasco. Thereafter, ring opening of **4** was conducted in $NaOCH_3$ in DMF at room temperature, which after usual work up gave desired product in excellent yield. Under this condition, the reaction was not reversible and even no trace of starting material was observed on TLC (Table 1). It was interesting to note that the change of solvent from methanol to DMF provided excellent results. We contemplated that the recyclization is more facile in polar protic solvent rather than in polar aprotic solvent. Thus, DMF was found as a choice of solvent for better yields and clean reaction.

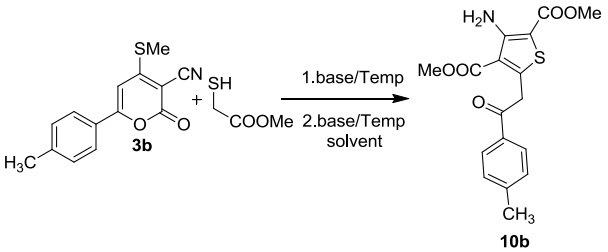
Mechanistically, the ring opening of **4** is initiated with attack of methoxide ion at carbonyl carbon at C4 to form a transition state which stabilized after ring opening to form tetrasubstitutedthiophene (**10)**. If reaction was not monitored carefully, the formed product **10** in methanol in the presence of methoxide ion cyclized to parent compound **4** in significant amount (Scheme 5).

Scheme 5: A plausible mechanism for the ring opening and ring closure



After success of two steps strategy for the synthesis of tetrasubstituted thiophenes, our prime objective was to synthesize **10** in single step using 2-pyranones as a precursor. For one pot synthesis of **10**, optimization of reaction was carried out in various solvents and bases. We conducted our screening by refluxing a mixture of **3b** and methyl thioglycolate in methanol using triethyl amine (1.0 mmol) as a base for 24 h which exclusively delivered thieno[3,2-*c*]pyrans (**4**). This indicated that methanol only acts as solvent in the reaction and not as nucleophile (entry 1, Table 2). In other set of experiment, a mixture of lactone **3b**, methyl thioglycolate and triethyl amine in methanol was refluxed at 90 °C for 2.5 h. Tereafter, sodium methoxide was added and reaction mixture was stirred further at room temperature for 1.5 h. Usual work-up delivered 60 % of desired product (Table 2, entry 2). In another set of experiment, pyranothiophene formed by the reaction of **3b** and methyl thioglycolate using triethyl amine in methanol, sodium methoxide was added and ring opening was performed at 90 °C. This reaction afforded 62 % of desired producand stirred further for two t (entry 3, Table 2). In quest for better yield and to avoid reversibility of the reaction, we performed a reaction of **3b** and methyl thioglycolate in the presence of $NaOCH_3$ and DMF at 90°C, which produced a complex mixture (entry 4, Table 2). In another set of experiment, we performed the reaction using Et_3N in DMF at room temperature for 40 h and thereafter sodium methoxide was added and stirred further for additional 2 h at

Table:2. Optimization of reaction conditions[a,b,d]



Entry	Solvent	Base 1/t, °C/T, h	Base 1/t, °C/T, h	Yield (%)
1.	CH_3OH	Et_3N/rt/24 h	-	-[c]
2.	CH_3OH	Et_3N/90/2.5 h	$NaOCH_3$/rt/1.5	60
3.	CH_3OH	Et_3N/90/2.5 h	$NaOCH_3$/90/1	62
4.	DMF	$NaOCH_3$/90/2h	$NaOCH_3$/90/4	Complex mixture
5	DMF	Et_3N/rt/40 h	$NaOCH_3$/rt/2	80
6.	DMF	Et_3N/90/2.5 h	$NaOCH_3$/rt/2	86

[a]Reactions were carried out by stirring 3b (0.5 mmol), methylthioglycolate (0.75 mmol), triethyl amine (1.0 mmol) and sodium methoxide (1.0 mmol) at various temperature; [b]1st and 2nd bases were added sequentially and reaction was carried out for given time at mentioned temperature; [c]thieno[3,2-*c*]pyran was isolated; [d]room temperature was ranging between 30-35 °C

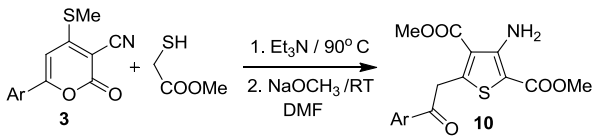
room temperature. Usual work up afforded 80 % of tetrasubstituted thiophene (**10**) (entry 5, Table 2). To reduce the duration of reaction, A mixture of **3b** and methylthioglycolate was stirred in the presence of triethyl amine as a base in DMF at 90 °C for 2.5 h to generate pyranothiophene *in situ*. Thereafter, NaOMe was added and stirred further at room temperature. Usual work up delivered 86 % of the desired product **10** (entry 6, Table 2).

After optimization of reaction condition, we have synthesized various derivatives of tetrasubstituted thiophene in good to excellent yields in one pot. It was interesting to note that methyl 3-amino-6,7-diaryl-4-oxo-4*H*-thieno[3,2-*c*]pyran-2-carboxylates (**4**) under similar reaction conditions did not form tetrasubstituted thiophene, possibly the presence of additional aryl group at position 6 stabilized the pyran ring and not allow the ring opening from alkoxide ion.

The presence of various functional group in aryl ring present at position 6 of 2-pyranone does not follow any specific trend on reactivity. The presence of 4-nitrophenyl and 4-bromophenyl ring greatly reduces the yield of tetrasubstituted thiophenes. Overall, it is very difficult to assess the role of aryl ring in the reaction.

The molecular view (ORTEP) for the compounds **10a** with atom numbering scheme is presented in Figure 2.[ξ] The compound crystallizes in monoclinic crystal system having P_12_1/C_1 space group with four molecules in the unit cell. The dihedral angle between the two aromatic rings *viz.* thiophene and the phenyl ring is 76.89°. The torsion angles O(1)-C(7)-C(1)-C(6) and O(1)-C(7)-C(8)-C(9) are 170.29(17)° and 30.9(2)°, respectively. The torsion

Scheme 6: One pot approach for the synthesis of tetrasubstituted thiophenes **10**



10a) Ar=C_6H_5; 87%
10b) Ar=*p*-$CH_3.C_6H_4$; 86%
10c)Ar=*p*-$F.C_6H_4$; 85%
10d)Ar=*p*-$Cl.C_6H_4$; 68%
10e)Ar=*o*-$Cl.C_6H_4$; 70%
10f)Ar=*p*-$Br.C_6H_4$; 62%
10g)Ar=*m*-$Br.C_6H_4$; 55%
10h)Ar=2-naphthyl; 83%
10i)Ar=1-naphthyl; 80%
10j)Ar=*p*-$OCH_3.C_6H_4$; 80%
10k)Ar= *3,4-*$(OCH_3)_2.C_6H_4$; 80%
10l)Ar=*o*-$OCH_3.C_6H_4$; 75%
10m) Ar=2-Theinyl; 70%
10n) Ar=2-Furyl; 77%
10o) Ar=*p*-$NO_2.C_6H_4$; 65%

angles associated with the two ester functions and the 1° amine group *viz.* N(1)-C(13)-C(14)-C(15), C(11)-C(10)-C(13)-N(1), C(13)-C(10)-C(11)-O(3) and C(13)-C(14)-C(15)-O(4) are 0.9(3), –0.6(3), -1.4(3) and -3.2(3), respectively. These torsion angle data indicates that N(1), O(4) and O(3) are almost coplanar and the two hydrogens over 1° amine can display intramolecular hydrogen bonding.

Figure 2: ORTEP diagram of **10a** at 30% probability with atom numbering scheme

The intramolecular N(1)–H(1′)···O3 and N(1)–H(1′′)···O4 interaction distances and angles are 2.09(2) Å; 130(2)° and 2.21(2) Å; 129(2)°, respectively (Fig. 3). The supramolecular aggregation in **10a** is stabilized by a pair of weak intermolecular N−H···O interactions (Fig. 3) that lead to the formation of centrosymmetric dimers. The N(1)−H(1′′)···O intermolecular interaction distance is 2.199 Å and the < N−H···O is non-linear having magnitude of 130.74°.

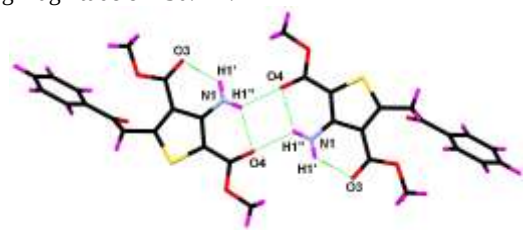


Fig. 3: Centro symmetric dimer held by pair of weak N−H···O interactions (intramolecular N−H···O interaction pairs are also presented).

The analysis of the interaction energy in the crystal structures of **10a** by means of dimer unit bound by pair of N-H···O interactions at the DFT level of theory yields the interaction energy –20.82 kJ/mol for pair of interaction and –10.41 kJ/mol for individual N-H···O interaction. To confirm further the nature of these weak interactions, bond critical points (bcp) were calculated for the different dimers by using the Atoms in Molecules theory.[37] The bond critical points observed between the interacting atoms, confirmed the presence of weak non-covalent interactions between the two molecules of **10**. The value of electron density (ρ); Laplacian of the electron density ($\nabla^2\rho_{bcp}$); bond ellipticity (ε) electron density (ρ) and total energy density (H) at the bond critical point for all the three interactions are presented in Table 3. As indicated in the table, the electron density for all the three types of interactions at bond critical point (ρ_{bcp}) are less than +0.10 au which indicates a closed shell hydrogen bonding interactions. Additionally, the Laplacian of the electron density $\nabla^2\rho_{bcp}$ in all the three cases are greater than zero which indicated the depletion of electron density in the region of contact between the H···O atoms. The bond ellipticity (ε) which measures the extent to which the electron density is preferentially accumulated in a given plane containing the bond path indicates that all the three interactions are not cylindrically symmetrical in nature.

Table 3: Selected topographical features for various interactions computed at B3LYP/6-31G** level of theory.

Interaction Type	ρ_{bcp}	$\nabla^2\rho_{bcp}$	E	H (au)
Intra N–H···O	+0.016769	+0.056219	+0.100692	+0.029323
Intra N–H···O	+0.025872	+0.081472	+0.023475	+0.028191
Inter N–H···O	+0.014931	+0.054220	+0.088161	+0.018966

Conclusions

One pot an expeditious, economical and convenient synthesis of dimethyl 3-amino-5-(2-oxo-2-arylethyl)thiophene-2,4-dicarboxylates has been developed for the first time through [3+2] donor-acceptor heteroannulation of 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles and methyl thioglycolate followed by ring opening using sodium methoxide. We have also demonstrated the ring opening reaction of dimethyl 3-amino-5-(2-oxo-2-arylethyl)thiophene-2,4-dicarboxylate in methanol and DMF and given some interesting finding. If we perform ring opening in methanol rather than DMF, it was observed that prolonged stirring reverted to parent compound **4**. The various functional groups present of thiophene ring at positions 2,3,4,5 are very reactive and can be utilized as precursors for the construction of various fused heterocycles not easily obtainable by conventional route. The mild reaction conditions, easy workup and non-involvement of metal catalyst make this protocol attractive for practical applications.

Experimental Section

General remarks: Commercially available reagents and solvents were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on 400MHz and 100MHz NMR spectrometer respectively. $CDCl_3$ were used as solvent for NMR. Chemical shift reported in ppm considering ($CDCl_3$)δ 7.24 ppm for ^{1}H

NMR and δ 77.00 ppm for ^{13}C NMR as an internal standard. Signal patterns are indicated as s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; br s, broad singlet. Coupling constants (*J*) are given in hertz (Hz). Infrared (IR) spectra were recorded on AX-1 spectrophotometer and reported as wave number (cm^{-1}). Intensity data for **10** were collected at 298(2) K on a Sapphire2-CCD, OXFORD diffractometer system equipped with graphite monochromated Mo Kα radiation λ = 0.71073 Å. The final unit cell determination, scaling of the data, and corrections for Lorentz and polarization effects were performed with CrysAlis RED.[38] The structures were solved by direct methods (SHELXS-97)[39] and refined by a full-matrix least-squares procedure based on F^2.[40] All the calculations were carried out using WinGX system Ver-1.64.[41] All non-hydrogen atoms were refined anisotropically; hydrogen atoms were located at calculated positions and refined using a riding model with isotropic thermal parameters fixed at 1.2 times the U_{eq} value of the appropriate carrier atom.

General procedure for the synthesis of dimethyl 3-amino-5-(2-oxo-2-(aryl)ethyl)thiophene-2,4-dicarboxylate: Two steps and one pot approach were established.

***One pot synthetic approach (Method A)*:** A mixture of 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles (0.5 mmol), methyl thioglycolate (0.75 mmol) and triethylamine (1.0 mmol) in DMF (4.0 mL) was stirred for 2.5 h at 90 ^oC. Thereafter, the reaction mixture was brought to room temperature and sodium methoxide (1.0 mmol) was added to the reaction mixture and stirred for additional 2 h at room temperature. The reaction mixture was poured onto crushed ice with vigorous stirring followed by neutralization with 10% HCl. The precipitate obtained was filtered, dried and recrystallized from methanol to obtain the desired product in good to excellent yields.

Ring opening Approach in Methanol (Method B): Methyl 3-amino-6-arylthieno[3,2-*c*]pyran-4-one-2-carboxylates (4, 0.5mmol) obtained by the procedure reported[33] earlier was treated with freshly prepared $NaOCH_3$ solution (23 mg Na in 4.0 ml MeOH) for 1-2 h and completion of reaction was monitored by TLC. After completion, the excess of methanol was removed under reduced pressure followed by addition of cold water. Reaction mixture was neutralized with 10% HCl and filtered the precipitate. The crude product was purified by silica gel column chromatography using 50% dichloromethane in hexane as an eluent.

Ring opening Approach in DMF (Method C): A mixture of methyl 3-amino-6-arylthieno[3,2-*c*]pyran-4-one-2-carboxylates (4, 0.5 mmol) and sodium methoxide (1.0 mmol) in DMF (4.0 mL) was stirred for 1-2 h at room temperature. Completion of reaction was monitored by TLC. Thereafter, the reaction mixture was poured onto crushed ice with vigorous stirring followed by neutralization with 10% HCl. The precipitate obtained was filtered dried and recrystallized from methanol to obtain the pure product.

Dimethyl 3-amino-5-(2-oxo-2-phenylethyl)thiophene-2,4-dicarboxylate (10a): Yield: 87 % (144 mg) R_f = 0.32 (1:1 hexane in dichloromethane); yellow solid; mp: 142-144 ^oC; IR (KBr): 3476, 3365, 1685, 1597, 1448, 1326 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.62 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.66 (s, 2H, CH_2), 6.83 (br s, 2H, NH_2), 7.49 (t, *J* = 7.62 Hz, 2H, ArH), 7.58-7.59 (m, 1H, ArH), 7.98 (d, *J* = 7.32 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.6, 51.2, 51.4, 117.8, 128.0, 128.7, 133.5, 136.2, 151.1, 155.1, 163.4, 164.2, 194.3; HRMS (ESI): calculated for $C_{16}H_{15}NO_5S$, 334.0744 (M+ H^+) found for *m/z*, 334.0741.

Dimethyl 3-amino-5-(2-oxo-2-(*p*-tolyl)ethyl)thiophene-2,4-dicarboxylate (10b): Yield: 86 % (144 mg) R_f = 0.31 (1:1 hexane in dichloromethane); white solid; mp: 162-164 ^oC; IR (KBr): 3478, 3359, 1702, 1687, 1579, 1274 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H, CH_3), 3.61 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.64 (s, 2H, CH_2), 6.83 (br s, 2H, NH_2), 7.28 (d, *J* = 7.93 Hz, 2H, ArH), 7.88 (d, *J* = 7.93 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 40.5, 51.1, 51.3, 97.7, 117.7, 128.1, 129.4, 133.7, 144.3, 151.3, 155.1, 163.4, 164.2, 193.9; HRMS (ESI): calculated for $C_{17}H_{17}NO_5S$, 348.0900 (M+ H^+); found for *m/z*, 348.0891.

Dimethyl 3-amino-5-(2-(4-fluorophenyl)-2-oxoethyl)thiophene-2,4-dicarboxylate (10c): Yield: 85 % (149 mg) R_f = 0.21 (1:1 hexane in dichloromethane); yellow solid; mp: 152-153 ^oC; IR (KBr): 3476, 3359, 1702, 1595, 1528, 1273 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.63 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.60 (s, 2H, CH_2), 6.82 (br s, 2H, NH_2), 7.16 (t, *J* = 8.77 Hz, 2H ArH), 8.00-8.02 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.5, 51.2, 51.4, 115.9, (d, *J* = 22.04 Hz), 117.8, 124.9, 128.4, 130.7, (d, *J* = 9.58 Hz), 132.6, 150.8, 155.0, 163.3, 164.1, 165.9 (d, *J* = 255.9), 192.8; HRMS (ESI): calculated for $C_{16}H_{14}FNO_5S$, 352.0649 (M+ H^+); found for *m/z*, 352.0648.

Dimethyl 3-amino-5-(2-(4-chlorophenyl)-2-oxoethyl)thiophene-2,4-dicarboxylate (10d): Yield: 68 % (124 mg) R_f = 0.30 (1:1 hexane in dichloromethane); white solid; mp: 147-149 ^oC; IR (KBr): 3482, 3363, 1701, 1589, 1459, 1273 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.63 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.63 (s, 2H, CH_2), 6.82 (br s, 2H, NH_2), 7.46 (d, *J* = 8.54 Hz, 2H ArH), 7.93 (d, *J* = 8.54 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.5, 51.2, 51.5, 117.8, 129.1, 129.5, 134.5, 140.0, 150.6, 155.0, 163.3, 164.2, 193.2; HRMS (ESI) calculated for $C_{16}H_{14}ClNO_5S$, 368.0354 (M+ H^+); found for *m/z*, 368.0348

Dimethyl 3-amino-5-(2-(2-chlorophenyl)-2-oxoethyl)thiophene-2,4-dicarboxylate (10e): Yield: 70 % (128 mg) R_f = 0.30 (1:1 hexane in dichloromethane); cinnamon solid; mp: 90 ^oC; IR (KBr): 3461, 3348, 1707, 1664, 1587, 1269 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.69 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.65 (s, 2H, CH_2), 6.82 (br s, 2H, NH_2), 7.34-7.36 (m, 1H, ArH), 7.38-7.45 (m 2H, ArH), 7.53-7.55 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.6, 51.2, 51.5, 117.8, 127.02, 129.5, 130.7, 131.0, 132.2, 138.2, 150.0, 155.0, 163.4, 164.2, 196.6; HRMS (ESI): calculated for $C_{16}H_{14}ClNO_5S$, 368.0354 (M+ H^+); found for *m/z*, 368.0352.

Dimethyl 3-amino-5-(2-(4-bromophenyl)-2-oxoethyl)thiophene-2,4-dicarboxylate (10f): Yield: 62 % (127 mg) R_f = 0.28 (1:1 hexane in dichloromethane); yellow solid; mp: 141-143 ^oC; IR (KBr): 3475, 3359, 1699, 1599, 1458, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.63 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.62 (s, 2H, CH_2), 6.82 (br s, 2H, NH_2), 7.63 (d, *J* = 8.54 Hz, 2H ArH), 7.85 (d, *J* = 8.54 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.5, 51.2, 51.5, 117.8, 128.7, 129.6, 132.1, 134.9, 150.6, 155.0, 163.3, 164.1, 193.4; HRMS (ESI) calculated

for $C_{16}H_{14}BrNO_5S$, 411.9849 (M+ H^+); found for *m/z*, 411.9840.

Dimethyl 3-amino-5-(2-(3-bromophenyl)-2-oxoethyl)thiophene-2,4-dicarboxylate (10g): Yield: 55 % (112 mg) R_f = 0.24 (1:1 hexane in dichloromethane); chocolate solid; mp: 134 ^oC; IR (KBr): 3467, 3350, 1699, 1582, 1517 1270 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.65 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.63 (s, 2H, CH_2), 6.82 (br s, 2H, NH_2), 7.37 (t, *J* = 7.63 Hz, 1H, ArH), 7.72 (d, *J* = 9.92 Hz, 1H, ArH); 7.91 (d, *J* = 7.63 Hz, 1H, ArH), 8.11-8.12 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.6, 51.2, 51.5, 117.9, 123.1, 126.6, 130.3, 131.1, 136.3, 137.9, 150.4, 155.0, 163.3, 164.1, 193.0; HRMS (ESI) calculated for $C_{16}H_{14}BrNO_5S$, 411.9849 (M+ H^+); found for *m/z*, 411.9839.

Dimethyl 3-amino-5-(2-(naphthalen-2-yl)-2-oxoethyl)thiophene-2,4-dicarboxylate (10h): Yield: 83 % (158 mg) R_f = 0.21 (1:1 hexane in dichloromethane); carrot orange solid; mp: 170-172 ^oC; IR (KBr): 3476, 3361, 1702, 1586, 1529, 1274 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.59 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.80 (s, 2H, CH_2), 6.85 (br s, 2H, NH_2), 7.56-7.62 (m, 2H, ArH), 7.87-8.02 (m, 4H, ArH), 8.53 (s,1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.7, 51.2, 51.4, 117.8, 123.7, 126.9, 127.8, 128.7, 129.5, 129.8, 132.4, 133.5, 135.7, 151.2, 155.1, 163.4, 164.2, 194.2; HRMS (ESI): calculated for $C_{20}H_{17}NO_5S$, 384.0900 (M+ H^+) found for *m/z*, 384.0895.

Dimethyl 3-amino-5-(2-(naphthalen-1-yl)-2-oxoethyl)thiophene-2,4-dicarboxylate (10i): Yield: 80 % (153 mg) R_f = 0.22 (1:1 hexane in dichloromethane); buff solid; mp: 151-153 ^oC; IR (KBr): 3459, 3346, 1706, 1686, 1586, 1273 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.58 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.74 (s, 2H, CH_2), 6.86 (br s, 2H, NH_2), 7.50-7.55 (m, 3H, ArH), 7.87 (d, *J* = 8.24 Hz, 1H, ArH); 7.99 (dd, *J* = 7.33 Hz, 7.79 Hz, 2H, ArH), 8.56 (d, *J* = 8.24 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.8, 51.2, 51.5, 117.8, 124.2, 125.6, 126.6, 127.6, 128.2, 128.4, 130.0, 133.2, 133.9, 134.7, 151.0, 163.5, 164.2, 197.5; HRMS (ESI) calculated for $C_{20}H_{17}NO_5S$, 384.0900 (M+ H^+) found for *m/z*, 384.0900.

Dimethyl 3-amino-5-(2-(4-methoxyphenyl)-2-oxoethyl)thiophene-2,4-dicarboxylate (10j): Yield: 80 % (144 mg) R_f = 0.17 (1:1 hexane in dichloromethane); yellow solid; mp: 142-144 ^oC; IR (KBr): 3475, 3353, 1700, 1582, 1451, 1278 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.62 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.61 (s, 2H, CH_2), 6.82 (br s, 2H, NH_2), 6.95 (d, *J* = 8.54 Hz, 2H ArH), 7.96 (d, *J* = 9.16 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.3, 51.2, 51.4, 55.5, 113.9, 117.7, 129.2, 130.4, 151.6, 155.1, 163.5, 163.7, 164.2, 192.8; HRMS (ESI) calculated for $C_{17}H_{17}NO_6S$, 364.0849 (M+ H^+); found for *m/z* 364.0847.

Dimethyl 3-amino-5-(2-(3,4-dimethoxyphenyl)-2-oxoethyl)thiophene-2,4-dicarboxylate (10k): Yield: 80 % (157 mg) R_f = 0.18 (1:1 hexane in dichloromethane); buff solid; mp: 183-184 ^oC; IR (KBr): 3475, 3345, 1707, 1590, 1512, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3) 4.64 (s, 2H, CH_2), 6.82 (br s, 2H, NH_2), 6.91 (d, *J* = 8.39 Hz, 1H, ArH), 7.52-7.53 (m, 1H, ArH), 7.62-7.64 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.2, 51.1, 51.4, 55.9, 56.0, 110.0, 110.1, 117.7, 122.7, 129.3, 149.1, 151.6, 153.5, 155.0, 163.4, 164.2, 192.9; HRMS (ESI): calculated for $C_{18}H_{19}NO_7S$, 394.0955 (M+ H^+); found for *m/z*, 394.0947.

Dimethyl 3-amino-5-(2-(2-methoxyphenyl)-2-oxoethyl)thiophene-2,4-dicarboxylate (10l): Yield: 75 % (136 mg) R_f = 0.18 (1:1 hexane in dichloromethane); yellow solid; mp: 115-117 ^oC, IR (KBr): 3471, 3354, 1690, 1586, 1508, 1274 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.61 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.63 (s, 2H, CH_2), 6.83 (br s, 2H, NH_2), 6.97-7.02 (m, 2H, ArH), 7.48 (t, *J* = 7.63 Hz, 1H, ArH), 7.70 (d, *J* = 7.63 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.6, 51.1, 51.2, 55.4, 97.4, 111.4, 117.5, 120.7, 127.2, 130.5, 134.0, 152.1, 155.2, 158.5, 163.5, 164.2, 196.0; HRMS (ESI): calculated for $C_{17}H_{17}NO_6S$, 364.0849 (M+ H^+); found for *m/z*, 364.0847.

Dimethyl 3-amino-5-(2-oxo-2-(thiophen-2-yl)ethyl)thiophene-2,4-dicarboxylate (10m): Yield: 70 % (118 mg) R_f = 0.33 (1:1 hexane in dichloromethane); white solid; mp: 145-147 ^oC; IR (KBr): 3481, 3365, 1685, 1589, 1439, 1272 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.59 (s, 2H, CH_2), 6.83 (br s, 2H, NH_2), 7.15 (dd, *J* = 4.88, 4.88 Hz, 1H, Ar-H), 7.67 (d, *J* = 4.27 Hz, 1H, ArH), 7.78 (dd, *J* = 1.22 ,1.49 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.2, 51.2, 51.4, 117.8, 128.2, 132.1, 134.1, 143.0, 150.2, 163.4, 164.2, 187.0; HRMS (ESI): calculated for $C_{14}H_{13}NO_5S_2$,340.03068 (M+ H^+); found for *m/z* 340.0307.

Dimethyl 3-amino-5-(2-(furan-2-yl)-2-oxoethyl)thiophene-2,4-dicarboxylate (10n): Yield: 77 % (124 mg) R_f = 0.25 (1:1 hexane in dichloromethane); yellow colored solid; mp: 149-151 ^oC; IR (KBr): 3481, 3363, 1701, 1587, 1466, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.53 (s, 2H, CH_2), 6.56 (m,1H, Ar-H), 6.82 (br s, 2H, NH_2), 7.25 (d, *J* = 3.66 Hz, 1H, ArH),7.61 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.2, 51.2, 51.4, 112.5, 117.4, 117.8, 146.5, 150.0, 151.9, 155.0, 163.4, 164.2, 183.3; HRMS (ESI): calculated for $C_{14}H_{13}NO_6S$, 324.0536 (M+ H^+); found for *m/z*, 324.0536

Dimethyl 3-amino-5-(2-(4-nitrophenyl)-2-oxoethyl)thiophene-2,4-dicarboxylate (10o): Yield: 65 % (122 mg) R_f = 0.17 (1:1 hexane in dichloromethane); yellow solid; mp: 194-196^oC; IR (KBr): 3467, 3363, 1699, 1608, 1530, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.61 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.64 (s, 2H, CH_2), 6.74 (br s, 2H, NH_2), 8.09-8.11 (m, 2H, ArH), 8.28-8.30 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.1, 51.3, 51.6, 118.0, 124.0, 129.1, 140.7, 149.8, 150.5, 163.2, 164.1, 193.0; HRMS (ESI): calculated for $C_{16}H_{14}N_2O_7S$, 379.0594 (M+ H^+); found for *m/z*, 379.0594.

Acknowlegements

Authors thank Council of Scientific and Industrial Research (CSIR, New Delhi) and Department of Science and Technology (DST, New Delhi) Delhi and ICMR New Delhi for financial support. SNS, PY, RP thank University Grants Commission (UGC, New Delhi) and SS thank Council of Scientific and Industrial Research (CSIR, New Delhi) for research fellowship. Authors thank University of Delhi for providing research funding and instrumentation facility.

Notes and references

[a]*Department of Chemistry, University of Delhi, North campus, Delhi, India-110007; Tel:+911127666646;E-mail: ramendrapratap@gmail.com*

[b]*Department of Chemistry, University of Lucknow, Lucknow, Uttar Pradesh, India-226009.*
[c]*Division of SAIF, Central Drug Research Institute, Lucknow, Uttar Pradesh, India-226001*

† Electronic Supplementary Information (ESI) available: [This material includes ^{1}H and ^{13}C NMR spectra for all the reported compounds]. See DOI: 10.1039/b000000x/

ξ Crystal data for **10a** (CCDC 1038008): $C_{16}H_{15}NO_5S$, formula mass 333.35, monoclinic space group $P1_21/C_1$, a = 14.073(5), b = 13.465(5), c = 8.576(5) Å, β = 93.433(5)º, V = 1622.2(13) Å^3, Z = 4, d_{calcd} = 1.365 mg m^{-3}, linear absorption coefficient 0.224 mm^{-1}, F(000) = 696, crystal size 0.27 × 0.25 × 0.18 mm, reflections collected 9249, independent reflections 3729 [R_{int} = 0.0232], Final indices [I> 2σ(I)] R_1= 0.0466 wR_2= 0.1110, R indices (all data) R_1= 0.0628, wR_2= 0.1207, gof 1.042, Largest difference peak and hole 0.233 and -0.232 e Å^{-3}.

1. T. Eicher, S. Hauptmann and A. Speicher,*The Chemistry of Heterocycles*, Wiley-VCH, New York, 2003, ch. 5, section 5.6; (b) R. K. Russell and J. B. Press, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees, E. W. F. Scriven and A. Padwa, Pergamon Press, New York, 1996, vol. 2, pp. 679–729; (c) N. Fokialakis, C. L. Cantrell, S. O. Duke, A. L. Skaltsounis, D. E. Wedge, *J. Agric. Food Chem.*, 2006, **54**, 1651-1655; (d) C. Medower, L. Wen, W. W. Johnson, *Chem. Res. Toxicol.*, 2008, **21**, 1570-1577.
2. C. Valant, L. Aurelio, S. M. Devine, T. D. Ashton, J. M. White, P. M. Sexton, A. Christopoulos, P. J. Scammells, *J. Med. Chem*., 2012, **55**, 2367-2375.
3. H. Lutjens, A. Zickgraf, H. Figler, J. Linden, R. A. Olsson, P. J. Scammells, *J. Med. Chem.*, 2003, **46**, 1870-1877.
4. Q. Huang, P. F. Richardson, N. W. Sach, J. Zhu, K. K. C. Liu, G. L. Smith, D. M. Bowles, *Org. Process Res. Dev*., 2011, **15**, 556-564.
5. V. Oza, S. Ashwell, L. Almeida, P. Brassil, J. Breed, C. Deng, T. Gero, M. Grondine, C. Horn, S. Ioannidis, D. Liu, P. Lyne, N. Newcombe, M. Pass, J. Read, S. Ready, S. Rowsell, M. Su, D. Toader, M. Vasbinder, D. Yu, Y. Yu, Y. Xue, S. Zabludoff, J. Janetka, *J. Med. Chem.*, 2012, **55**, 5130-5142.
6. K. E. Schulze, P. R. Cohen, B. R. Nelson, *.Dermatol. Surg*., 2006, **32**, 407–410.
7. T. B. McMurry, *DNA Repair*, 2007, **6**, 1161-1169.
8. N. P. Dolman, J. C. A. More, A. Alt, J. L. Knauss, O. T. Pentikäinen, C. R. Glasser, D. Bleakman, M. L. Mayer, G. L. Collingridge, D. E. Jane, *J. Med. Chem.*, 2007, **50** , 1558-1570.
9. H. Zeybek, *Turk Veteriner Hekimleri Dernegi Dergisi*, 1970, **40**, 11–17.
10. B. Roth, C. Cheng, Diaminopyrimidines, in Progress in Medicinal Chemistry (Eds. G.B.Ellis and G.E.D West), *Elsevier Biomedical Press, New York* **Vol.19**, pp 267, 1982.
11. M.S.A.E.A. El-Gaby, S.G. Abdel-Hamide, M.M. Ghorab, S.M. El-Sayed, *Acta Pharm*., 1999, **49**, 149-158.
12. C. R. Petrie, H. B. Cottam, P. A. McKernan, R. K. Robins, G. R. Revankar, *J. Med. Chem.*, 1985, **28**, 1010-1016.
13. M. N. Nasr, M. M. Gineinah, *Arch. Pharm*., 2002, **335**, 289-295.
14. Bristol-Myers Squibb. http://www.bms.com.
15. M. Muccini, *Nat. Mater*., 2006, **5**, 605–613.
16. A. Mishra, C.Q. Ma, P. Bauerle, *Chem. Rev*., 2009, **109**, 1141–1276.
17. T. Noda, H. Ogawa, N. Noma, Y. Shirota, *Adv. Mater.*, 1997, 720-722.
18. (a) R. P. Ortiz, J. Casado, V. Hernández, J.T.L Navarrete, J. Letizia, M. Ratner, A. Facchetti, T. Marks, *Chem. Eur. J.*, 2009, **15**, 5023-5039; (b) B. Ong, Y. Wu, Y. Li, P. Liu, H. Pan, *Chem. Eur. J.*, 2008, **14**, 4766-4778.
19. P. Dario, A. Marco, G. Giuseppe, C. Roberto, Z. R. Margherita, L. Guglielmo, B. Giovanna, F. Laura, *Appl. Phys. Lett*., 2002, **81**, 3534–3536.
20. (a) A. Zen, A. Bilge, F. Galbrecht, R. Alle, K. Meerholz, J. Grenzer, D. Neher, U. Scherf, T. Farrell, *J. Am. Chem. Soc*., 2006, **128**, 3914–3915; (b) C.Q. Ma, E. Mena-Osteritz, T. Debaerdemaeker, M. M. Weink, R. A. J. Janssen, P. Bauerle *Angew. Chem., Int. Ed*., 2007, **46**, 1679–1683.
21. Y. Ie, Y. Umemoto, M. Okabe, T. Kusunoki, K. I. Nakayama, Y. J. Pu, J. Kido, H. Tada, Y. Aso, *Org. Lett.*, 2008, **10** , 833-836; (b) Y. Ie, M. Nitani, M. Ishikawa, K. I. Nakayama, H. Tada, T. Kaneda, Y. Aso, *Org. Lett.*, 2007, **9**, 2115-2118.
22. Y. Huang, A. Dömling, *Mol. Diversity*, 2011, **15**, 3−33; (b) K. Gewald, E. Schinke, H. Bottcher, *Chem. Ber*., 1966, **99**, 94−100. (c) K. Gewald, *Angew. Chem*., 1961, **73**, 114−118.
23. L. Knorr, *Ber. Dtsch. Chem., Ges*. 1885, **18**, 299−311; (b) C. Paal, *Ber. Dtsch. Chem. Ges*., 1885, **18**, 367−371; (c) C. Paal, *Ber. Dtsch. Chem. Ges*., 1885, **18**, 2251−2254.
24. R. Mishra, K. K. Jha, S. Kumar, I. Tomer *Pharma Chem*., 2011, **3**,38−54.
25. I. Yavari, Z. Hossaini, M. Sabbaghan, *Tetrahedron Lett.*, 2008, **49**, 844-846.
26. (a) M. M. El-Saghiera, F. S. Matoughb, M. F. Farhatb, N. A. Salehb, K. M. Kreddanc, S. O. El-Tierb, H. B. Hussienc, *Jardon J. Chem*., 2008, **3**, 223-232. (b) A.M.M. El-Saghier, *Molecules*, 2002, **7**, 756-766.
27. L. W. Singh, H. Ila, H. Junjappa, *J. Chem. Soc. Perkin Trans. 1*, 1988, 2365-2368; (b) M. Augustin, W. Z. Dolling, *Chem*., 1981, **21**, 216-217; (c) A. Dutta, H. Illa, H. Junjappa *Synthesis*, 1988, 556-557; (d) A. Thomas, G. Singh, H. Illa, H. Junjappa, *Tetrahedron Lett*., 1989, **30**, 3093-3096; (e) D. Thomae, G. Kirsch, P. Seck, *Synthesis*, 2007, 1027-1032; (f) R. Samual, P. Chandran, S. Retnamma, K. A. Sasikala, N. K. Sreedevi, E. R. Anabha, C. V. Asokan, *Tetrahedron*, 2008, **64**, 5944-5948.
28. G. Sathishkannan, K. Srinivasan, *Chem.Commun*., 2014, **50**, 4062-4064.
29. T. Okazawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc*., 2002, **124**, 5286-5287.
30. H. S. Lee, S. H. Kim, J. N. Kim, *Tetrahedron Lett*., 2009, **50** , 6480-6483.
31. G. C. Nandi, S. Samai, M. S. Singh, *J. Org. Chem*., 2011, **76** , 8009-8014.
32. L. R. Wen, T. He, M. C. Lan, M Li, *J. Org. Chem*., 2013, **78** , 10617-10628.
33. (a)P. Mishra, H. K. Maurya, B. Kumar, V. K. Tandon, V. J. Ram, *Tetrahedron Lett.*, 2012, **53** , 1056-1059; (b) S. N. Sahu, M. K. Gupta, T. Jadhav, P. Yadav, S. Singh, R. Misra, R. Pratap, *RSC adv.* 2014, **4**, 56779.
34. Y. Tominaga, A. Ushirogochi, Y. Matsuda, G. Kobayashi, *Chem.Pharm. Bull*, 1984, **32**, 3384-3395.
35. V. Macháček, V. Štěrba, H. Collect. Czech. Zahradníčková *Chem. Commun*., 1981, **46**, 3097-3103.
36. V. J. Ram, A. Goel, P. K. Shukla, A. Kapil, *Bioorg. Med.Chem. Lett.*, 1997, **7** , 3101-3106.
37. R. F. W. Bader *Atoms in Molecules: A Quantum Theory Oxford University Press*: New York, 1990.
38. CrysAlis CCD, RED *(version 1.711.13), copyright* 1995-2003, Oxford Diffraction Poland Sp.
39. G. M. Sheldrick *SHELXS-97*, Program for Crystal Structure Solution, University of Göttingen, Göttingen, 1997.
40. G. M. Sheldrick, *SHELXL-97*, Program for Crystal Structure Refinement, University of Göttingen, Göttingen, 1997.
41. L. J. Farrugia, WinGX suite for small-molecule single–crystal crystallography. *J. Appl. Crystallogr*., 1999, **32**, 837-838.
42. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr, T. Vreven, K. N. Kudin, J. C. Burant, Gaussian 03, revision D. 01. *Gaussian Inc., Wallingford, CT* 2004, **26**.
43. (a) A. D. Becke, *J. Chem. Phys*., 1993, **98**, 5648-5652; (b) C. T. Lee, W. T. Yang, R. G. Parr, *Phys. Rev. B: Condens. Matter Mater. Phys*., 1998, **37**, 1133-1138.
44. S. F. Boys, F. Bernardi, *Mol. Phys*., 1970, **19**, 553-556.
1.