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A Novel and Expedient Approach to New Heterocycles Containing Benzothiophene, Benzothieno[2,3-*d*]pyrimidine and Coumarin Moieties

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Abstract: In order to obtain potent protein-tyrosine kinase inhibitors, a novel and versatile method for synthesis of heterocyclic compounds **4a–d** and **5a–c** comprising 2-imino-2*H*-1-benzopyran, tetrahydrobenzo[*b*]thiophene, and carboxamide/1*H*-benzimidazole fragments has been developed. This method was based on the reactions of 2-imino-2*H*-1-benzopyrans **1a,b** and **2** with 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophenes **3a–c** in glacial acetic acid. Furthermore, new heterocycles **8a,b** with tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine and coumarin moieties have been synthesized *via* a rearrangement of the corresponding 2-(tetrahydrobenzo[*b*]thien-2-yl)imino-2*H*-1-benzopyran-3-carboxamides **4a,b**.

Keywords: benzopyrans; benzothienopyrimidines; benzothiophenes; rearrangements; imidic acids and derivatives

Introduction

Within the last years new structural classes of tyrosine kinase inhibitors have been found which exhibit tremendous improvements in potency and specificity over prior compounds. Most of these newer compounds are directed against either the epidermal growth factor (EGF) or platelet derived growth factor (PDGF) receptor tyrosine kinases and have the capacity to effectively suppress their target in cells. Interesting chemical classes of EGF receptor tyrosine kinase inhibitors are compounds comprising coumarin,[1] imidazole,[2-4] benzothienopyrimidine or thiophene[3-7] moieties. Recently a series of compounds possessing imidazole,[8] thiophene,[9] and benzopyran[10] fragments were synthesized and screened for inhibitory activity against PDGF receptor tyrosine kinase. There are also several reports of significance with regard to nonreceptor kinases. For example, 3-carbamoyl-2-imino-2*H*-1-benzopyran derivatives were synthesized and their inhibitory effects on tyrosine kinase $pp60^{c\text{-}src}$ and $p56^{lck}$ were evaluated.[11-13] Another compound having a thieno-fragment that shows potent activity against $p56^{lck}$ tyrosine kinase is methyl 3-(*N*-isothiazolone)-2-thiophenecarboxylate.[14,15]

As part of our current program on structure-activity relationship (SAR) studies of different heterocycles, we were especially interested in a short and selective entry into heterocyclic compounds comprising (imino/oxo)benzopyran, tetrahydrobenzo[*b*]thiophene, and carboxamide/benzimidazole segments as potential tyrosine kinase inhibitors. We also required to prepare tetrahydrobenzo[*b*]thienobenzopyrans **4a,b** (*cf.* Scheme 2) as intermediates for synthesis of new tetrahydrobenzothieno[2,3-*d*]pyrimidines of type **8** (*cf.* Scheme 3).[16] In this paper we report the successful synthesis of a number of 3-substituted 2-(tetrahydrobenzo[*b*]thien-2-yl)imino-2*H*-1-benzopyrans **4** and **5** and 2-(coumarin-3-yl)tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-ones **8**.

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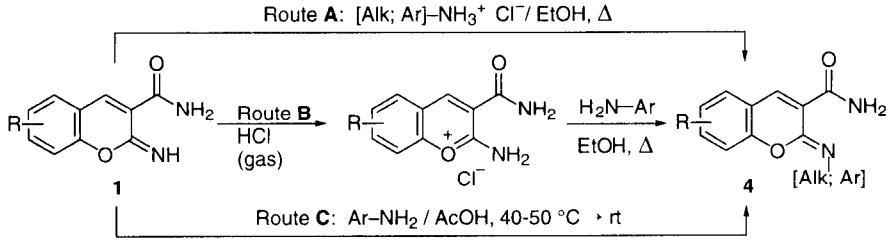
Results and Discussion

In our approach to synthesis of heterocyclic compounds of type **4** and **5** (*cf.* Scheme 2), we envisioned that this class of compounds could be derived from readily available 2-imino-2*H*-1-benzopyrans **1** and **2** and 3-substituted 2-aminotetrahydrobenzo[*b*]thiophenes **3a–c**.

One of the synthetic routes to 2-arylaminothiophenes[17] is based on reactions of 2-aminothiophenes with arylamines and their salts in ethanol.[18,19] A similar approach was applied for synthesis of 2-hydroxyiminocoumarins.[20,21] In a recent report from our laboratory[22] it was shown that a variety of 2-aryl- and 2-alkyl-substituted iminocoumarins **4** could be prepared by routes A and B as presented in Scheme 1. The method for synthesis of these compounds is based on cyclic imido ester aminolysis involving nucleophilic attack on a C=N carbon and subsequent decomposition of the tetrahedral intermediate. The mechanism of reactions for simple imidates and amines has been studied by Jencks.[23] This type of reaction should be also similar to acidic hydrolysis of iminocoumarins to coumarins which proceeds through the formation of the corresponding benzopyrylium salts.[24]

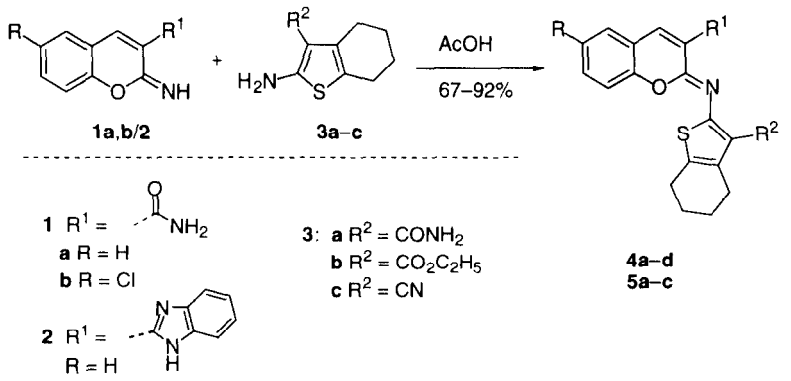


Scheme 1

The principal feature of the methods for synthesis of 2-*N*-substituted iminobenzopyrans **4** is using either hydrochloride salts of amines (Scheme 1, route A)[20-22] or preparing benzopyrylium salts (Scheme 1, route B).[22] A drawback of the route B is that benzopyrylium salts of this type were particularly difficult to handle as they are *highly lacrymatory and sternutatory*. One obstacle to be also overcome is the presence of benzimidazole fragment in compound **2** possessing another basic nitrogen that makes a preparation of the 3-benzimidazolyl-benzopyrylium salt problematic. Moreover, the diprotonated form of compound **2** is extremely prone to hydrolysis to the corresponding oxo derivative.[25] However, it was shown that the imino group in compound **2** is more basic than the benzimidazolyl group and, under mild acidic conditions, formation of the 2-amino-3-(1*H*-benzimidazol-2-yl)-1-benzopyrylium salt takes place at first.[25] We found that the methods described above for synthesis of 2-*N*-substituted iminobenzopyrans were unsuitable for preparation of more complex structures of type **4** and **5** due to other side reactions and because of the poor solubility of the reactants.

To solve these problems, we advocate a different methodology, expeditious and safe, based on *in situ* formation of the corresponding salts, their reaction and subsequent removal of ammonia released. It is rationalized by the fact that there usually is a pH optimum for aminolysis of imido esters. However, to achieve a reaction proceeding optimally at a given pH, it is not always necessary to know the value of this pH. Rather, one may continuously change the pH, starting at a value at which the rate of disappearance of the starting material is very low, and proceeding at a rate of change which allows the desired reaction to go to completion before one has scanned through the useful pH region.

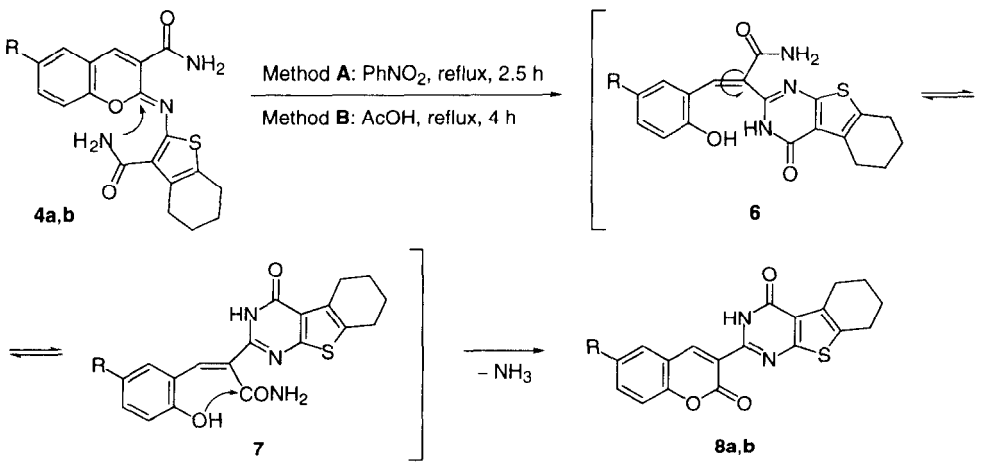
As a result of our extensive studies, we found a method based on using *glacial acetic acid*. Its function is 3-fold: i) as a solvent which increases the solubility of components; ii) as a protonating agent; and iii) as a reactant which binds the ammonia produced. In the beginning we performed model studies to synthesize known 2-*N*-arylsubstituted iminobenzopyrans of type **4**[22] starting from 2-imino-2*H*-1-benzopyran-3-carboxamides and arylamines and got excellent results (Scheme 1, route C)[26] by using glacial acetic acid.



Scheme 2. Reactions between 2-imino-2*H*-1-benzopyrans **1** and **2** and different heterocyclic amines **3** in glacial acetic acid

As shown in Scheme 2, synthesis of the desired thienoiminobenzopyrans **4a–d** and **5a–c** was finally achieved by adding equivalent amounts of the corresponding iminobenzopyran derivatives **1** or **2** to a warm solution of 3-substituted 2-aminothiophenes **3a–c** in glacial acetic acid. After stirring the reaction mixture at room temperature for *ca.* 12 hours, products were precipitated from the solution and subsequently isolated by filtration.

In our recent communication[27] we introduced a novel method for synthesis of compounds containing pyrimidine and coumarin units – 2-(2-oxo-2*H*-1-benzopyran-3-yl)-3*H*-quinazolin-4-ones. It was based on a rearrangement of 2-imino-2*H*-1-benzopyran-3-carboxamides **1** by the action of anthranilic acid as *N*-nucleophile. In our synthetic approach to required heterocycles of type **8** with benzothienopyrimidine and coumarin fragments, we applied the same strategy, but varied the methodology. It was found that 2-(*N*-3-carbamoyl-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)imino-2*H*-1-benzopyran-3-carboxamides **4a,b** have the capability to rearrange on refluxing in appropriate solvents (Method A and B, Scheme 3) to the corresponding 2-(coumarin-3-yl)-5,6,7,8-tetrahydro-3*H*-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-ones **8a,b**.

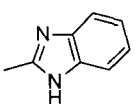
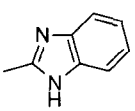
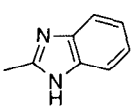


Scheme 3. Rearrangement of thienoiminobenzopyrans **4a,b** into tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidines **8a,b**

The best yields (53–67%) of the desired compounds **8** were obtained when glacial acetic acid was utilized as a solvent (Method B, Scheme 3). A possible mechanism of coumarin and pyrimidine formation *via* a rearrangement of **4a,b** is shown in Scheme 3. It involves intramolecular nucleophilic attack of NH_2 on C(2) of iminolactone ring in compounds **4**, iminolactone ring opening (**4** → **6**), and *E/Z* thermal isomerization of intermediates **6** (**6** ⇆ **7**) with subsequent cyclization of **7** to **8**. This type of thermal transformation of thienoiminobenzopyrans **4a,b** is a new and efficient pathway to biologically important compounds **8** comprising tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine and coumarin fragments.

The structures of compounds synthesized were assigned by analysis of mass, ^{1}H NMR, and IR spectra. The structure of compound **8b** was additionally corroborated by X-ray diffraction (Figure 1, Table 2).[36] Physicochemical data and methods for purification for compounds **4a–d**, **5a–c** and **8a,b** are given in Table 1.

Table 1. Physicochemical data of the synthesized 3-substituted 2-*N*-(3-R^2-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)imino-2*H*-1-benzopyrans **4a–d**, **5a–c** and 2-(2-oxo-2*H*-1-benzopyran-3-yl)-5,6,7,8-tetrahydro-3*H*-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-ones **8a,b**

Compd	R	R^1	R^2	Yield (%) (Method)	Recryst. solvent	Mp (°C)
4a	H	$CONH_2$	$CONH_2$	83	[a]	> 300
4b	Cl	$CONH_2$	$CONH_2$	92	[a]	273-274
4c	H	$CONH_2$	$CO_2C_2H_5$	67	DMF/*i*-PrOH	208-210
4d	H	$CONH_2$	C≡N	75	DMF/*i*-PrOH	286-287
5a	H		$CONH_2$	68	DMF/*i*-PrOH	283-284
5b	H		$CO_2C_2H_5$	79	DMF/*i*-PrOH	197-198
5c	H		C≡N	71	DMF/*i*-PrOH	280 (dec.)
8a	H	—	—	51 (A) 67 (B)	*i*-PrOH	267-268
8b	Cl	—	—	45 (A) 53 (B)	*i*-PrOH	242-243

[a] Compounds **4a,b** in solvents with high boiling points (*e.g.*, BuOH, DMF) undergo a rearrangement with formation of tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidines **8a,b** and they were purified by boiling in ethanol and then in chloroform.

Conclusions

We have presented a facile route for the formation of novel heterocycles comprising 2-imino-2*H*-1-benzopyran, tetrahydrobenzo[*b*]thiophene, and carboxamide/1*H*-benzimidazole fragments by the reaction of 2-

imino-2*H*-1-benzopyrans with 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophenes in glacial acetic acid. Moreover, compounds having benzothienopyrimidine and coumarin moieties have been conveniently prepared by utilizing the capability of the corresponding benzothienoiminobenzopyrans to rearrange on refluxing in appropriate solvents. The synthetic approaches thus allowed the efficient and practical preparation of required heterocycles for further biological studies with minimal synthetic effort and might open a new avenue for the synthesis a variety of heterocyclic systems of biological significance.

Experimental

Melting points (°C) were measured with a Büchi melting point apparatus and were uncorrected. Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F-254). ^{1}H NMR spectra were recorded on Varian WXR-400 or Bruker AMX-400 spectrometers in DMSO-d_6 or CF_3CO_2D + $CDCl_3$ using TMS as an internal standard (chemical shifts in ppm). Mass spectra were obtained with Finnigan MAT-4615B spectrometer at an ionization potential of 70 eV. Combustion analyses of all new compounds synthesized gave satisfactory microanalytical data. Infrared spectra were recorded in KBr pellets on an IBM 486 computer-controlled Specord M-80 spectrometer. 2-Imino-2*H*-1-benzopyran derivatives **1a**,[28,29] **1b**,[30] and **2**[31,32] were prepared according to reported methods by condensing 2-cyanoacetamide or (1*H*-benzimidazol-2-yl)acetonitrile[33] with salicylic aldehydes to form the expected imino compounds **1** and **2** using piperidine as a catalyst in ethanol at room temperature. 2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide **3a**,[34] ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate **3b**,[35] and 3-cyano-2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene **3c**[35] were synthesized by the application of Gewald reaction, namely, reactions of cyclohexanone with nitriles having an active methylene group in the α-position afforded substituted nitriles which undergo a facile cyclization with sulfur in the presence of diethylamine to give the thiophenes **3a–c**.

Synthesis of 3-substituted 2-N-(3-R²-4,5,6,7-tetrahydrobenzo[b]thien-2-yl)imino-2H-1-benzopyrans **4a–d** *and* **5a–c**

General procedure:

To a well-stirred warm (65–70 °C) solution of 3-substituted 2-amino-4,5,6,7-tetrahydrobenzo[*b*] thiophenes **3a–c** (4 mmol) in 15 mL of glacial acetic acid was added equivalent amount of the corresponding 2-imino-2*H*-1-benzopyran derivatives **1** or **2**. The reaction mixture was stirred at room temperature for *ca.* 12 h. The products, which precipitated in the course of the reactions, were filtered, washed with isopropanol (5 mL) and ether (2 x 12 mL), and recrystallized from the proper solvents. Yields and physicochemical data of the 3-substituted 2-*N*-(3-R²-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)imino-2*H*-1-benzopyrans **4a–d** and **5a–c** are listed in Table 1.

2-N-(3-Carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl)imino-2H-1-benzopyran-3-carboxamide (**4 a**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (br s, 1H, CONH_2); 8.33 (s, 1H, *H-4*); 7.87 (br s, 1H, CONH_2); 7.84 (br s, 1H, CONH_2); 7.79 (dd, 1H, J = 7.8, 1.4 Hz, *H-5*); 7.64 (ddd, 1H, J = 8.6, 8.2, 1.4 Hz, *H-7*); 7.48 (d, 1H, J = 8.2 Hz, *H-8*); 7.36 (dd, 1H, J = 8.6, 7.8 Hz, *H-6*); 7.31 (br s, 1H, CONH_2); 2.74 (br t, 2H, J = 5.0 Hz, CH_2); 2.66 (br t, 2H, J = 5.0 Hz, CH_2); 1.76 (m, 4H, CH_2-CH_2). MS *m/z* 367 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3343s, 3163m, 2936m, 2927m, 2917m, 2843w, 1656vs, 1628s, 1605s, 1590s, 1564m, 1547m, 1468m, 1454m, 1435m. Anal. Calcd. for $C_{19}H_{17}N_3O_3S$ (367.43): C, 62.11; H, 4.66; N, 11.44; S, 8.73. Found: C, 62.29; H, 4.47; N, 11.67; S, 8.49.

2-N-(3-Carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl)imino-6-chloro-2H-1-benzopyran-3-carboxamide (**4b**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91 (br s, 1H, CONH_2); 8.27 (s, 1H, *H-4*); 7.88 (d, 1H, J = 1.4 Hz, *H-5*); 7.81 (br s, 1H, CONH_2); 7.79 (br s, 1H, CONH_2); 7.61 (dd, 1H, J = 8.0, 1.4 Hz, *H-7*); 7.44 (d, 1H, J = 8.0 Hz, *H-8*); 7.26 (br s, 1H, CONH_2); 2.74 (br t, 2H, J = 5.8 Hz, CH_2); 2.66 (br t, 2H, J = 5.0 Hz, CH_2); 1.76 (m, 4H, CH_2-CH_2). MS *m/z* 403, 401 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3371s, 3184s, 3050w, 2930m, 2882w, 2839w, 1715w, 1657s, 1640ws, 1632s, 1586ws, 1562s, 1540m, 1239. Anal. Calcd. for $C_{19}H_{16}ClN_3O_3S$ (401.87): C, 56.79; H, 4.01; N, 10.46; S, 7.98. Found: C, 56.29; H, 4.07; N, 10.68; S, 7.79.

2-N-(3-Ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl)imino-2H-1-benzopyran-3-carboxamide (**4c**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.56 (br s, 1H, CONH_2); 8.50 (s, 1H, *H-4*); 7.54 (dd,1H, J = 7.8, 1.6 Hz, *H-5*); 7.52 (br s, 1H, CONH_2); 7.51 (ddd,1H, J = 8.3, 7.3, 1.6 Hz, *H-7*); 7.28 (d, 1H, J = 8.3 Hz, *H-8*); 7.26 (dd, 1H, J = 7.8, 7.3 Hz, *H-6*); 4.26 (q, 2H, J = 7.0 Hz, $CO_2CH_2CH_3$); 2.52 (m, 4H, CH_2 & CH_2); 1.76 (m, 4H, CH_2-CH_2); 1.27 (t, 3H, J = 7.0 Hz, $CO_2CH_2CH_3$). MS *m/z* 396 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3250s, 3135m, 3120m, 3106m, 2975m, 2936m, 2920m, 2840m, 1704w, 1682vs, 1628w, 1591s, 1576s, 1562m, 1544m, 1456m, 1440m. Anal. Calcd. for $C_{21}H_{20}N_2O_4S$ (396.47): C, 63.62; H, 5.08; N, 7.07; S, 8.09. Found: C, 63.47; H, 5.17; N, 6.92; S, 8.22.

2-N-(3-Cyano-4,5,6,7-tetrahydrobenzo[b]thien-2-yl)imino-2H-1-benzopyran-3-carboxamide (**4d**): ^{1}H NMR (400 MHz, CF_3CO_2D + $CDCl_3$): δ 8.65 (s, 1H, *H-4*); 7.62 (m, 2H, *H-5* & *H-7*); 7.42 (d, 1H, J = 8.0 Hz, *H-8*); 7.32 (dd, 1H, J = 7.8, 7.3 Hz, *H-6*); 2.68 (m, 2H, CH_2); 2.58 (m, 2H, CH_2); 1.80 (m, 4H, CH_2-CH_2); CONH_2 exchanged with solvent deuterium. MS *m/z* 349 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3407s, 3392s, 3271m, 3152m, 3286m, 3055m, 2937m, 2871w, 2840w, 2215m, 1733m, 1716m, 1676vs, 1651m, 1624m, 1590vs, 1578vs, 1560s, 1454m. Anal. Calcd. for $C_{19}H_{15}N_3O_2S$ (349.41): C, 65.31; H, 4.33; N, 12.03; S, 9.18. Found: C, 65.37; H, 4.19; N, 11.91; S, 9.04.

3-(1H-Benzimidazol-2-yl)-2-N-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl)imino-2H-1-benzopyran (**5a**): ^{1}H NMR (400 MHz, CF_3CO_2D + $CDCl_3$): δ 8.65 (s, 1H, *H-4*); 7.74 (m, 2H, Ar*H*); 7.60 (m, 2H, Ar*H*); 7.50 (m, 2H, Ar*H*); 7.40 (d, 1H, J = 8.3 Hz, *H-8*); 7.31 (dd, 1H, J = 7.8, 7.3 Hz, *H-6*); 2.70 (m, 2H, CH_2); 2.65 (m, 2H, CH_2); 1.80 (m, 4H, CH_2-CH_2); N*H* & CONH_2 exchanged with solvent deuterium. MS *m/z* 440 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3350m, 3319s, 3261m, 3193m, 3176m ,3056m, 2931m, 2855w, 1639s, 1626s, 1608s, 1583m, 1564s, 1452w, 1419w. Anal. Calcd. for $C_{25}H_{20}N_4O_2S$ (440.53): C, 68.16; H, 4.58; N, 12.72; S, 7.28. Found: C, 67.81; H, 4.69; N, 12.32; S, 7.06.

3-(1H-Benzimidazol-2-yl)-2-N-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl)imino-2H-1-benzopyran (**5b**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.66 (br s, 1H, N*H*); 7.76 (dd, 1H, J = 7.8, 1.6 Hz, *H-5*); 7.64 (m, 2H, Ar*H*); 7.55 (ddd, 1H, J = 7.8, 7.3,1.6 Hz, *H-7*); 7.46 (d, 1*H*, J = 8.3 Hz, *H-8*); 7.34 (dd, 1H, J = 7.8, 7.3 Hz, *H-6*); 7.20 (m, 2H, Ar*H*); 4.44 (q, 2H, J = 7.0 Hz, $CO_2CH_2CH_3$); 1.84 (br m, 4H, CH_2 & CH_2); 1.42 (t, 3H, J = 7.0 Hz, $CO_2CH_2CH_3$); 1.41 (m, 4H, CH_2-CH_2). MS *m/z* 469 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3168vs, 3136m, 2976w, 2935m, 2877w, 2863w, 1704w, 1686m, 1658w, 1632m, 1591m, 1577w, 1540w, 1455w. Anal. Calcd. for $C_{27}H_{23}N_3O_3S$ (469.57): C, 69.06; H, 4.94; N, 8.95; S, 6.83. Found: C, 68.90; H, 4.66; N, 8.88; S, 6.77.

3-(1H-Benzimidazol-2-yl)-2-N-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thien-2-yl)imino-2H-1-benzopyran (**5c**): ^{1}H NMR (400 MHz, CF_3CO_2D + $CDCl_3$): δ 8.67 (s, 1H, H-4); 7.72 (m, 2H, Ar*H*); 7.60 (m, 2H, *H-5* & *H-7*); 7.52 (m, 2H, Ar*H*); 7.40 (d, 1H, J = 8.0 Hz, *H-8*); 7.29 (dd, 1H, J = 7.7, 7.3 Hz, *H-6*); 2.70 (m, 2H, CH_2); 2.65 (m, 2H, CH_2); 1.80 (m, 4H, CH_2-CH_2); N*H* & CONH_2 exchanged with solvent deuterium. MS *m/z* 422 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν3331s, 3312s, 2941s, 2871m, 2207m, 1631s, 1608w, 1589vs, 1576s, 1555m, 1516w. Anal.

Calcd. for $C_{25}H_{18}N_4OS$ (422.51): C, 71.07; H, 4.29; N, 13.26; S, 7.59. Found: C, 70.89; H, 4.07; N, 13.44; S, 7.78.

Synthesis of 2-(2-oxo-2H-1-benzopyran-3-yl)-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-ones **8a,b**

General procedures:

Method A: A solution of the corresponding benzothienobenzopyrans **8a,b** (1.5 mmol) in 10 mL of dry and degassed nitrobenzene was refluxed for 2.5 h. During the course of reaction, release of ammonia was observed. After reaction was completed (monitoring by TLC), the mixture was cooled and a precipitate was filtered, washed with cold isopropanol (2 x 5 mL) and recrystallized from the proper solvents.

Method B: A solution of the corresponding benzothienobenzopyrans **8a,b** (1.5 mmol) in 10 mL of glacial (99.8%) acetic acid was refluxed for 4 h. After reaction was completed (monitoring by TLC), the mixture was cooled and a precipitate was filtered, washed with cold isopropanol (2 x 5 mL) and recrystallized from the proper solvents.

Yields and physicochemical data of the synthesized 2-(2-oxo-2*H*-1-benzopyran-3-yl)-5,6,7,8-tetrahydro-3*H*-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-ones **8a,b** are listed in Table 1.

2-(2-Oxo-2H-1-benzopyran-3-yl)-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one (**8a**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (br s, 1H, N*H*); 9.00 (s, 1H, *H-4*); 8.04 (dd, 1H, *J* = 7.8, 1.6 Hz, *H-5*); 7.78 (ddd, 1H, *J* = 8.3, 7.3, 1.6 Hz, *H-7*); 7.56 (d, 1H, *J* = 8.3 Hz, *H-8*); 7.48 (dd, 1H, *J* = 7.8, 7.3 Hz, *H-6*); 2.91 (br t, 2H, *J* = 5.9 Hz, 8-CH_2); 2.78 (br t, 2H, *J* = 5.9 Hz, 5-CH_2); 1.81 (m, 4H, CH_2-CH_2). MS *m/z* 350 ($M^{+\cdot}$). Anal. Calcd. for $C_{19}H_{14}N_2O_3S$ (350.39): C, 65.13; H, 4.03; N, 7.99; S, 9.15. Found: C, 65.42; H, 3.99; N, 8.14; S, 8.91.

2-(6-Chloro-2-oxo-2H-1-benzopyran-3-yl)-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one (**8b**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.51 (br s, 1H, N*H*); 8.98 (s, 1H, *H-4*); 7.58 (d, 1H, *J* = 1.5 Hz, *H-5*); 7.50 (dd, 1H, *J* = 8.2, 1.5 Hz, *H-7*); 7.56 (d, 1H, *J* = 8.2 Hz, *H-8*); 2.91 (br t, 2H, *J* = 6.0 Hz, 8-CH_2); 2.68 (br t, 2H, *J* = 6.0 Hz, 5-CH_2); 1.77 (m, 4H, CH_2-CH_2). MS *m/z* 386, 384 ($M^{+\cdot}$). Anal. Calcd. for $C_{19}H_{13}ClN_2O_3S$ (384.84): C, 59.30; H, 3.40 N, 7.28; S, 8.33. Found: C, 59.59; H, 3.61 N, 7.43; S, 8.61.

X-ray Structure Analysis of **8b**:[36] red needles were obtained from isopropanol, $C_{19}H_{13}ClN_2O_3S$, FW = 384.84, triclinic, *a* = 14.378(5), *b* = 13.640(4), *c* = 8.701(3) Å, β = 98.07(3)°, V = 1689.4(10) Å^3, space group $P2_1/c$, Z = 4, D_c = 1.513 Mg m^{-3}, F(000) = 792, μ = 0.373 mm^{-1}. Data were measured using a Siemens P3/PC diffractometer, Mo-Kα radiation (λ = 0.71073 Å, graphite monochromator), and 2θ/θ-scans, with 5° ≤ 2θ ≤ 55°. Reflections collected: 1815, independent reflections: 1693 (R_{int} = 3.38%), and observed reflections with I › 3σ(I): 1000. Lorentz and polarization corrections were applied to the data-set. The structure was solved by direct method using SHELXL-86[37] and was refined by full-matrix least squares (based on F^2) using SHELXL-93.[38] The weighting scheme was ω = [σ^2 (F) + 0.0000F^1]$^{-1}$. Final R indices (obs. data): R_1 = 0. 0593, ωR_2 = 0.1066 and R indices (all data): R_1 = 0.1237, ωR_2 = 0.1263. Non-H atoms refined with anisotropic displacement parameters, H-atoms with isotropic displacement parameters. Fractional atomic coordinates with standard deviations (in parentheses) and equivalent isotropic temperature factors U(eq) are shown in Table 2. ORTEP drawing of **8b** is shown in Figure 1.

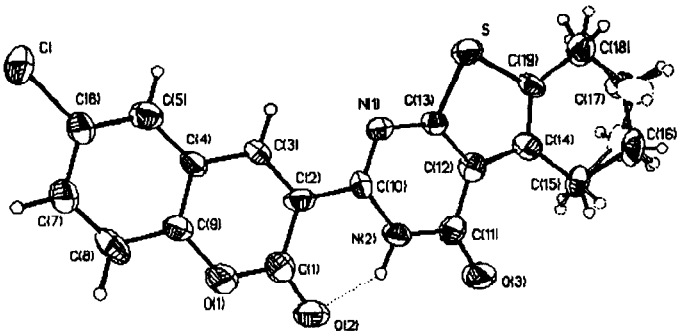


Figure 1. ORTEP drawing of the terahydrobenzothienopyrimidine **8b**

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for $C_{19}H_{13}ClN_2O_3S$. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	x	y	z	U(eq)
Cl	7748(1)	8436(2)	5675(3)	83(1)
S	2186(1)	9373(1)	10937(2)	62(1)
O(1)	5171(4)	5544(3)	7716(6)	71(2)
O(2)	4031(4)	5075(4)	8976(6)	83(2)
O(3)	1846(4)	5786(3)	11595(7)	83(2)
N(1)	3334(4)	8028(4)	9965(6)	45(2)
N(2)	3028(4)	6357(3)	10345(6)	46(2)
C(1)	4488(5)	5749(5)	8576(8)	61(2)
C(2)	4308(4)	6811(4)	8920(7)	42(2)
C(3)	4887(4)	7483(5)	8438(7)	51(2)
C(4)	5650(5)	7217(4)	7584(8)	47(2)
C(5)	6285(5)	7889(5)	7141(7)	49(2)
C(6)	6997(4)	7606(5)	6321(8)	48(2)
C(7)	7093(5)	6599(5)	6020(8)	60(2)
C(8)	6476(5)	5918(5)	6519(8)	59(2)
C(9)	5752(5)	6241(5)	7245(8)	57(2)
C(10)	3530(4)	7104(5)	9764(7)	38(2)
C(11)	2247(5)	6483(5)	11127(8)	57(2)
C(12)	2019(4	7525(5)	11278(7)	49(2)
C(13)	2588(4)	8190(4)	10696(7)	34(2)
C(14)	1259(5)	7947(5)	11954(8)	51(2)
C(15)	475(4)	7431(5)	12615(7)	53(2)
C(16)	–349(14)	8067(15)	12850(4)	66(8)
C(17)	–144(18)	9123(15)	13260(3)	94(10)
C(16A)	–96(16)	8150(19)	13400(3)	66(8)
C(17A)	–329(15)	8991(16)	12300(3)	94(10)
C(18)	535(5)	9617(5)	12342(8)	63(2)
C(19)	1242(4)	8949(4)	11798(7)	38(2)

References

1. Yang, E. B.; Zhao, Y. N.; Zhang, K.; Mack, P. *Biochem. Biophys. Res. Commun.* **1999**, *260*, 682.
2. (a) Rewcastle, G. W.; Palmer, B. D.; Bridges, A. J.; Showalter, H. D. H.; Li, S.; Nelson, J.; McMichael, A.; Kraker, A. J.; Fry, D. W.; Denny, W. A. *J. Med. Chem.* **1996**, *39*, 918; (b) Copp, B. R.; Fairchild, C. R.; Cornell, L.; Casazza, A. M.; Robinson, S.; Ireland, C. M. *J. Med. Chem.* **1998**, *41*, 3909.
3. Fry, D. W.; Bridges, A. J.; Kraker, A.J.; McMichael, A.; Nelson, M.; Denny, W.A. *Am. Assoc. Cancer Res.* **1995**, *36*, 689.
4. (a) A review on synthesis and pharmacological aspects of heterocycles possessing thieno-fragment: Pech, R.; Böhm, R. *Pharmazie* **1984**, *39*, 4 and (b) a review on recent advances in tyrosine kinase inhibitors: Fry, D. W. *Ann. Rep. Med. Chem.* **1996**, *31*, 151.
5. Bridges, A. J.; Zhou, H. R. *J. Heterocycl. Chem.* **1997**, *34*, 1163.
6. Bridges, A. J.; Denny, W. A.; Fry, D.; Kraker, A.; Meyer, R.; Rewcastle, G. W.; Thompson, A. M.; Showalter, H. D. H. *PCT Int. Appl. WO 9519970* (1995); *Chem. Abstr.* **1996**, *124*, 8840.
7. Brunton, V. G.; Kelland, L. R.; Lear, M. J.; Montgomery, G. J.; Robertson, J. H.; Robins, D. J.; Queen, J.; Workman, P. *Anti-Cancer Drug Des.* **1996**, *11*, 265.
8. Palmer, B. D.; Smaill, J. B.; Boyd, M.; Boschelli, D. H.; Doherty, A. M.; Hamby, J. M.; Khatana, S. S.; Kramer, J. B.; Kraker, A. J.; Panek, R. L.; Lu, G. H.; Dahring, T. K.; Winters, R. T.; Showalter, H. D. H.; Denny, W. A. *J. Med. Chem.* **1998**, *41*, 5457.
9. Boschelli, D. H.; Wu, Z. P.; Klutchko, S. R.; Showalter, H. D. H.; Hamby, J. M.; Lu, G. H.; Major, T. C.; Dahring, T. K.; Batley, B.; Panek, R. L.; Keiser, J.; Hartl, B. G.; Kraker, A. J.; Klohs, W. D.; Roberts, B. J.; Patmore, S.; Elliott, W. L.; Steinkampf, R.; Bradford, L. A.; Hallak, H.; Doherty, A. M. *J. Med. Chem.* **1998**, *41*, 4365.
10. Thomas, J. E.; Venugopalan, M.; Galvin, R.; Wang, Y.; Bokoch, G. M.; Vlahos, C. J. *J. Cell. Biochem.* **1997**, *64*, 182.
11. Huang, C.-K. *PCT Int. Appl. WO 9640670* (1996); *Chem. Abstr.* **1997**, *126*, 131382.
12. Huang, C.-K.; Wu, F.-Y.; Ai, Y.-X. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2423.
13. Burke, T. R.; Lim, B.; Marquez, V. E.; Li, Z. H.; Bolen, J. B.; Stefanova, I.; Horak, I. D. *J. Med. Chem.* **1993**, *36*, 425.
14. Tu, N. P.; Madar, D. J.; BaMaung, N. Y.; Zhou, X.; Wiedeman, P. E.; Sheets, M. P.; Ballaron, S. J.; Trevillyan, J. M.; Mollison, K. W.; Warrior, U.; Faltynek, C. R.; Donnely, J. B.; Putman, C. B.; Carter, G. W.; Luly, J. R.; Djuric, S. W. *Abstr. Pap. Am. Chem. Soc.* **1998**, *216*, U280.
15. Ballaron, S. J.; Sheets, M.; Mollison, K. W.; Warrior, U.; Faltynek, C.; Donnelly, J.; Putman, B.; Wiedeman, P.; Madar, D.; Tu, N.; Hajduk, P.; Djuric, S.; Luly, J.; Trevillyan, J. *FASEB J.* **1997**, *11*, A1338.
16. Preliminary report: Vasylyev, M. V.; Bilokin, Y. V.; Branytska, O. V.; Kovalenko, S. M.; Chernykh, V. P. *Heterocycl. Commun.* **1999**, *5*, 241.
17. For an excellent review on chemistry of aminothiophenes and its derivatives, see: Norris, R. K. "Aminothiophenes and Its Derivatives," in: Gronowitz, S. (Ed.), *Thiophene and Its Derivatives*. New York: John Wiley & Sons, Inc., 1985; The Chemistry of Heterocyclic Compounds, Vol. 44. Part 2, Chapter V, pp 631-799.
18. Schaefer, H.; Jablokoff, H.; Hentschel, M.; Gewald, K. *J. Prakt. Chem.* **1984**, *326*, 917.

19. Jablokoff, H.; Schaefer, H.; Gewald, K.; Hentschel, M. *Ger. (East) DD 220,960* (1985); *Chem. Abstr.* **1985**, *103*, 195990y.
20. Matlack, A. S. *Ger., Offen. 1,806,435* (1969); *Chem. Abstr.* **1970**, *72*, P4337z.
21. O'Callaghan, C. N. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1335.
22. Zubkov, V. A.; Kovalenko, S. N.; Chernykh, V. P.; Ivkov, S. M. *Khim. Geterotsikl. Soedin.* **1994**, 760; *Chem. Abstr.* **1995**, *122*, 187329.
23. Hand, E. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 3505.
24. Kuhn, R.; Weiser, D. *Angew. Chem.* **1957**, *69*, 371.
25. Karasev, A. A.; Lukatskaya, L. L.; Rubtsov, M. I.; Zhikol, E. K.; Yarmolenko, S. N.; Ponomarev, O. A. *Zh. Obshch. Khim.* **1995**, *65*, 1547; *Chem. Abstr.* **1996**, *124*, 342517p.
26. Bilokin, Y. V. 'unpublished results'.
27. Bilokin, Y. V.; Kovalenko, S. N.; Bylov, I. E.; Chernykh, V. P. *Heterocycl. Commun.* **1998**, *4*, 257 and references cited therein.
28. Schiemenz, G. P. *Chem. Ber.* **1962**, *95*, 483.
29. Czerney, P.; Hartmann, H. *J. Prakt. Chem.* **1981**, *323*, 691.
30. O'Callaghan, C. N. *Proc. R. Ir. Acad., Sect. B* **1977**, *77B*, 533.
31. Hammad, A.; El-Sayed, A. S.; Islam, I. E.; Shafik, N. *J. Chem. Soc. Pak.* **1990**, *12*, 292.
32. Gadalla, K. Z.; Hammad, M. *Bull. Natl. Res. Cent. (Egypt)* **1993**, *18*, 151.
33. Copeland, R. A. B.; Day, A. R. *J. Am. Chem. Soc.* **1943**, *65*, 1072.
34. Arya, V. P. *Indian J. Chem.* **1972**, *10*, 1141.
35. Gewald, K. *Z. Chem.* **1962**, *2*, 305.
36. Crystallographic data for the structure **8b** reported in this paper including tables of bond lengths and angles, torsion angles, lists of anisotropic displacement parameters, hydrogen coordinates and isotropic displacement parameters have been deposited with the Cambridge Crystallographic Data Centre (CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; WWW: http://www.ccdc.cam.ac.uk; e-mail: deposit@ccdc.cam.ac.uk) as a supplementary publication No. CCDC–115021 and copies of the data can be obtained on application to CCDC.
37. Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **1990**, *A46*, 467.
38. Sheldrick, G. M. SHELXL93. Program for Refinement of Crystal Structures. University of Göttingen, Germany, **1993**.