Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 10051–10057

TETRAHEDRON

Synthesis and combinatorial approach of the reactivity of 6- and 7-arylthieno[3,2-*d*][1,3]oxazine-2,4-diones

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Received 2 July 2003; revised 6 October 2003; accepted 7 October 2003

Abstract—This paper describes a general procedure for the synthesis of new substituted thiaisatoic anhydrides or 6- or 7-aryl-1*H*-thiéno[3,2-*d*]-[1,3]oxazine-2,4-diones **3a–j** and **4a–f**. They were synthesized in large scale under microwave heating conditions with high yields. The reactivity vs nucleophilic reagents of these compounds was studied and permitted to develop a simple combinatorial procedure to synthesize a library of new thiophene ureidoacids **7a–j** and **8a–j**.

1. Introduction

The anthranilic acid and isatoic anhydride are useful building blocks for the synthesis of numerous heterocycles with therapeutic interest.[1,2] Despite the thiophen ring is considered as a bioisoster of the benzene ring, the synthesis and chemistry of thiophene analogs of isatoic anhydride remains very poorly studied.[3–5] Fabis et al. recently described an efficient synthesis of 1*H*-thieno[3,2-*d*][1,3]-oxazine-2,4-dione **1** and 1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-diones **2** also named thiaisatoic anhydrides[6,7] (Fig. 1).

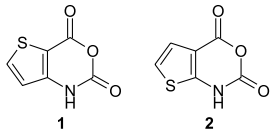

Figure 1.

Aiming at developing combinatorial strategies to design new heterocyclic libraries with potential therapeutic interest, we studied the synthesis of new 6- and 7-arylthieno[3,2-*d*][1,3]-oxazine-2,4-diones **3** and **4** and we started to explore these compounds as promising combinatorial scaffolds (Fig. 2).

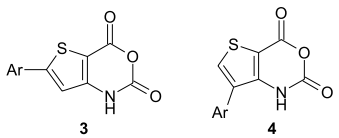

Figure 2.

Keywords: thieno[3,2-*d*][1,3]oxazine; isatoic acid; reactivity; ureidoacid; combinatorial chemistry; thiophene.
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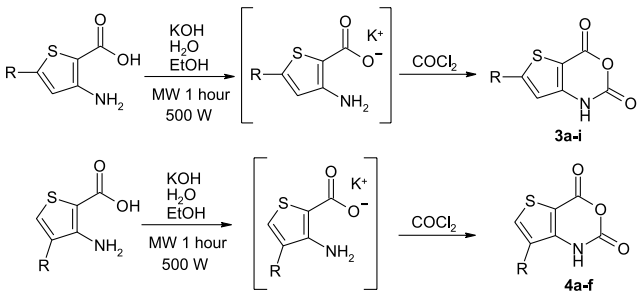
doi:10.1016/j.tet.2003.10.028

2. Results and discussion

2.1. Synthesis of anhydrides 3 and 4

The synthesis of anhydrides **3a–j** and **4a–f** started from the corresponding aminoesters prepared following a Kirsch method for 4-substituted aminoesters[8,9] or an Arnold–Vilsmeier–Haack method for the 5-substituted amino-esters.[10,11] According to our previously reported procedure, the alkaline hydrolysis of these aminoesters under micro-wave heating conditions led to the non isolated amino-carboxylate intermediates, and phosgene addition permitted us to isolate the corresponding anhydrides **3a–j** and **4a–f** in high yields (Scheme 1, Table 1). To our knowledge, only compound **3a** has been claimed in a patent.[12]



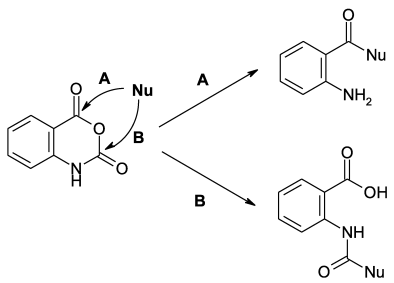
Scheme 1. Synthesis of substituted thiaisatoic anhydride.

2.2. Study of the reactivity of 3a–j and 4a–f

Bipolar reactivity of isatoic anhydride with nucleophiles is well-known and generally takes place on the carbonyl at position 4.[13] (Scheme 2, Way A) However, it was observed that 2-ureidobenzoic acid and 2-carbamoylbenzoic acid

Table 1.

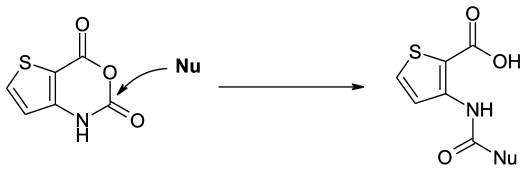
Compound	R=	Yields (%)	Compound	R=	Yields (%)
3a	Phenyl	73	**3i**	2-Thienyl	66
3b	4′-Fluorophenyl	82	**3j**	3-Thienyl	72
3c	4′-Chlorophenyl	75	**4a**	Phenyl	78
3d	4′-Bromophenyl	75	**4b**	4′-Fluorophenyl	80
3e	4-Tolyl	86	**4c**	4′-Chlorophenyl	76
3f	4′-Methoxyphenyl	78	**4d**	4′-Bromophenyl	73
3g	3′,4′-Dimethoxyphenyl	72	**4e**	4′-Methoxyphenyl	75
3h	3′,4′-Dichlorophenyl	75	**4f**	3′,4′-Dimethoxyphenyl	68



Scheme 2. Reactivity of isatoic anhydride.

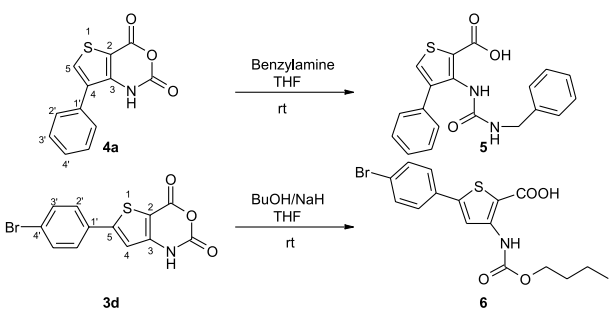
could be formed by using a large excess of reagent or under high temperature conditions.[14] (Scheme 2, Way B)

In the thiophene series, our previous works have shown that non substituted thiaisatoic anhydrides reacted with amines or alcohol to led only to 2-ureido and 2-carbamoylthiophene carboxylic acids, without traces of by-products (Scheme 3).



Scheme 3. Reactivity of thiaisatoic anhydride.

We then verified that 6- and 7-substituted thiaisatoic anhydrides **3d** and **4a** reacted respectively in the same manner as above with benzylamine or sodium butoxide at room temperature in THF to give the 2-ureidothiophenic acids **5** or the 2-carbamoylthiophenic acid **6** in high yields (Scheme 4).



Scheme 4. Reactivity of thiaisatoic anhydride.

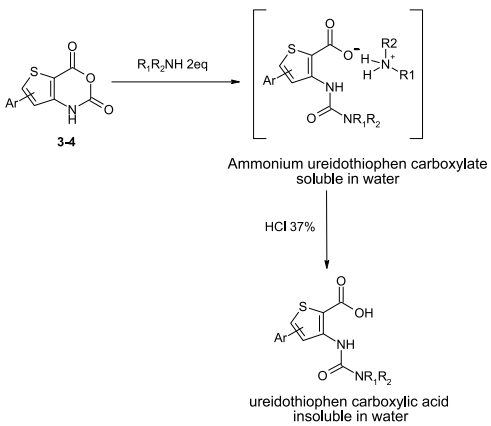
2.3. Reaction parallelization

In the light of these preliminary results we chose to develop the reactivity of substituted aryl thiaisatoic anhydrides with primary and secondary amines in a solution phase combinatorial approach to design libraries of ureidothiophene carboxylic acids.

The limitations of the solution phase combinatorial chemistry lies in the work up procedures and purification techniques. Within a few years, a number of purification methods have been developed for combinatorial solution phase chemistry among which, 'Fluorous work-up',[15] use of solution scavengers[16] or resin-bound scavengers[17] in order to purify the solution from reagent excess.

Our approach, that we named 'parallelization', was to simplify the reaction conditions to avoid tedious purification procedures. The bi-functionality and the reactivity of thiophene anhydrides with amines allowed us to use an acid/base procedure. We first replaced the solvent of the reaction by water in order to suppress the evaporation step. In these conditions the anhydrides reacted with 2.2 equiv. of amines in a water suspension to led the water soluble ammonium ureidocabocarboxylates. Subsequent acidification of the reaction mixture permitted to recover the ureidoacide as a precipitated solid after filtration. A straightforward washing with water discarded excess of amine as a water soluble hydrochloride (Scheme 4).

To verify strength and repeatability of our procedure, we realized two experimental tests under the above conditions. The first one was the reaction of anhydride **3c** with 10 amines, and the second one was the reaction of propylamine



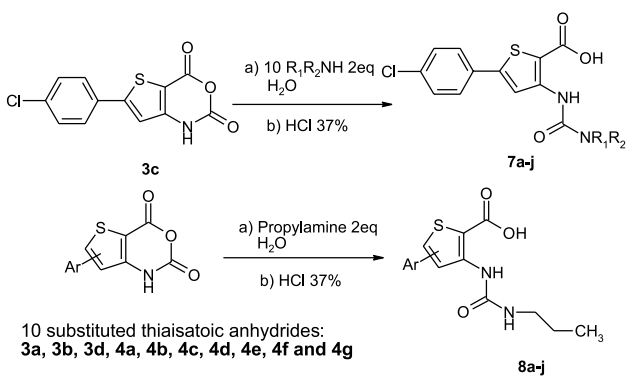
Scheme 5. Experimental optimization of the reaction.

Table 2.

Compounds	R_1R_2NH=	Yields (%)
7a	*N*-Benzylaniline	90
7b	Cyclopentylamine	92
7c	Phenylethylamine	89
7d	2,5-Dichloroaniline	88
7e	4-Methylpiperidine	93
7f	*n*-Butylamine	89
7g	Diisopropylamine	94
7h	Diethylamine	95
7i	Morpholine	88
7j	2-Chloroaniline	84

Table 3.

Compounds	Raw materials	Yields (%)
8a	**3a**	93
8b	**3b**	95
8c	**3c**	93
8d	**3d**	94
8e	**3e**	95
8f	**3f**	91
8g	**3g**	93
8h	**4a**	95
8i	**4b**	95
8j	**4d**	92



Scheme 6. Verification of reaction robustness and repeatability of our procedure.

with 10 anhydrides **3a**–**g** and **4a**–**c** (Scheme 5). The results are summarized in Tables 2 and 3 (Scheme 6).

In the two experiments the yields were up to 85% and the purity of the crude products was estimated as up to 80% by ^{1}H NMR.

3. Conclusion

This work has shown that substituted thiophene analogs of anhydride isatoic **3** and **4** could be synthesized on a multigram scale. Their reactivity with amines was studied in a combinatorial approach and the simplification of the experimental conditions permitted to design a small library of thiophene ureidoacids with high yields and good purity with an easy procedure. Fortified by these experiment, we will pursue the study of these combinatorial scaffolds and we are now able to produce thousands of 2-ureidothiophenic acids.

4. Experimental

4.1. General procedures

Commercial reagents were used as received without additional purification. Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were taken with a Genesis Series FTIR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL Lambda 400 Spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. The mass spectra (MS) were taken on a JEOL JMS GCMate spectrometer at a ionizing potential of 70 eV. Thin layer chromatography (TLC) was performed on a 0.2 mm precoated plates of silica gel 60F-264 (Merck). Visualization was made with ultraviolet light.

Primary and secondary amines were purchased from Acros Organics, Avocado, Lancaster and Aldrich and were used without further purification.

4.2. General procedures for the synthesis of substituted thiaisatoic anhydrides 3a–j and 4a–f

Methyl 3-amino-4-aryl- or methyl 3-amino-5-arylthiophene-2-carboxylates (15 g) was suspended in a hydroalcoholic (25/75) solution of potassium hydroxide (7N). The mixture was then refluxed with stirring under microwave heating conditions using a Normatron® microwave reactor (500 W) for 1 h. After cooling the solution at 0°C, gaseous phosgene was bubbled for 30 min in the aqueous solution with vigorous stirring until acidic pH. After addition, the mixture was allowed to stand at room temperature for 15 min. The precipitate was filtered, washed with water and with a saturated solution of sodium hydrogencarbonate solution. After drying the product was washed with diethyl ether to give **3a**–**j** and **4a**–**f**.

4.2.1. 6-Phenyl-2,4-dihydro-1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione (3a). White solid, mp>250°C, 73%. IR (KBr): 3418, 3055, 1792, 1758, 1458, 1004, 751, 713 cm^{-1}. ^{1}H NMR (*d6*-DMSO) δ 7.07 (s, 1H, H_4), 7.47 (m, 5H, Har), 11.53 (broad s, 1H, NH). ^{13}C NMR (*d6*-DMSO) δ 104.3, 113.2, 126.3, 129.5, 130.5, 131.6, 149.0, 150.6, 154.9, 155.5. MS (*m*/*z*) M$^+$=245 (75.6), 201 (100).

4.2.2. 6-(4′-Flurophenyl)-2,4-dihydro-1*H*-thieno[3,2-*d*]-[1,3]oxazine-2,4-dione (3b). White solid, mp=223°C, 82%. IR (KBr): 3369, 3092, 1786, 1757, 1463, 1003, 832, 713 cm^{-1}. ^{1}H NMR (*d6*-DMSO) δ 7.22 (s, 1H, H_4), 7.32 (dt, $^3J_{HH}$=8.3 Hz and $^3J_{HF}$=8.5 Hz, 2H, $H_{3'}$), 7.84 (dd, $^3J_{HH}$= 8.3 Hz and $^4J_{HF}$=5.7 Hz, 2H, $H_{2'}$), 11.82 (broad s, 1H, NH). MS (*m*/*z*) M$^+$=263 (31.7), 219 (100).

4.2.3. 6-(4′-Chlorophenyl)-2,4-dihydro-1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione (3c). Beige solid, mp>250°C, 75%. IR (KBr): 3278, 3054, 1793, 1733, 1457, 1003, 813 cm^{-1}. ^{1}H NMR (*d6*-DMSO) δ 7.22 (s, 1H, H_4), 7.51 (d, $^3J_{HH}$=7.2 Hz, 2H, $H_{3'}$), 7.76 (d, $^3J_{HH}$=7.2 Hz, 2H, $H_{2'}$), 11.20 (broad s, 1H). ^{13}C NMR (*d6*-DMSO) δ 104.6, 113.9, 123.7, 128.2, 130.9, 132.3, 149.1, 150.8, 153.2, 155.5. MS (*m*/*z*) M$^+$=281 (3.5), 279 (13), 237 (10.1), 235 (100).

4.2.4. 6-(4′-Bromophenyl)-2,4-dihydro-1*H*-thieno[3,2-*d*]-[1,3]oxazine-2,4-dione (3d). Pink solid, mp=231°C, 75%. IR (KBr): 3327, 3090, 1778, 1732, 1495, 990, 813, 753 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 7.20 (s, 1H, H_4), 7.63 (2d, $^3J_{HH}$=7.8 Hz, 4H, $H_{2'}$ and $H_{3'}$), 11.96 (broad s, 1H, NH). ^{13}C NMR (*d6*-DMSO) δ 104.7, 114.2, 128.1, 129.6, 130.8, 135.1, 149.4, 151.4, 153.2, 155.8. MS (*m/z*) M^+=325 (4.5), 323 (7.1), 281 (100), 279 (97.7).

4.2.5. 6-(4′-Tolyl)-2,4-dihydro-1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione (3e). Beige solid, mp>250°C, 86%. IR (KBr): 3424, 3080, 1792, 1745, 1462, 1002, 808, 706 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 2.33 (s, 3H, CH_3), 7.18 (s, 1H, H_4), 7.30 (d, $^3J_{HH}$=7.7 Hz, 2H, $H_{2'}$), 7.6 (d, $^3J_{HH}$=7.7 Hz, 2H, $H_{3'}$), 11.72 (broad s, 1H, NH). ^{13}C NMR (*d6*-DMSO) δ 20.9, 103.6, 112.8, 126.1, 129.0, 129.9, 140.3, 149.3, 151.3, 154.9, 155.6. MS (*m/z*) M^+=259 (43.5), 215 (100).

4.2.6. 6-(4′-Methoxyphenyl)-2,4-dihydro-1*H*-thieno[3,2-*d*]-[1,3]oxazine-2,4-dione (3f). White solid, mp=238°C, 78%. IR (KBr): 3337, 3078, 1778, 1722, 1492, 990, 821, 744 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 3.80 (s, 3H, OCH_3), 7.10 (d, $^3J_{HH}$=7.1 Hz, 2H, $H_{2'}$), 7.16 (s, 1H, H_4), 7.67 (d, $^3J_{HH}$=7.1 Hz, 2H, $H_{3'}$), 11.24 (broad s, 1H, NH). ^{13}C NMR (*d6*-DMSO) δ 55.4, 100.1, 102.9, 111.9, 114.8, 124.2, 127.8, 149.3, 151.2, 155.5, 161.0. MS (*m/z*) M^+=275 (74.8), 231 (100).

4.2.7. 6-(3′,4′-Dimethoxyphenyl)-2,4-dihydro-1*H*-thieno-[3,2-*d*][1,3]oxazine-2,4-dione (3g). White solid, mp> 250°C, 72%. IR (KBr): 3283, 3078, 1793, 1721, 1524, 997, 815, 688 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 3.82 (2s, 6H, $2OCH_3$), 7.01 (s, 1H, H_4), 7.13 (d, $^3J_{HH}$=8.4 Hz, 1H, $H_{2'}$), 7.24 (s, 1H, $H_{6'}$), 7.29 (d, $^3J_{HH}$=8.4 Hz, 1H, $H_{3'}$), 11.29 (broad s, 1H, NH). ^{13}C NMR (*d6*-DMSO) δ 55.6, 55.7, 102.6, 109.5, 112.4, 113.8, 119.1, 124.9, 149.1, 150.5, 151.0, 154.2, 154.9, 156.9. MS (*m/z*) M^+=305 (100), 261 (81.6).

4.2.8. 6-(3′,4′-Dichlorophenyl)-2,4-dihydro-1*H*-thieno-[3,2-*d*][1,3]oxazine-2,4-dione (3h). White solid, mp> 250°C, 75%. IR (KBr): 3401, 3088, 1784, 1728, 1481, 1032, 803, 768 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 7.30 (s, 1H, H_4), 7.69 (2d, $^3J_{HH}$=8.4 Hz, 1H, $H_{2'}$ and $H_{3'}$), 8.06 (s, 1H, $H_{6'}$), 11.37 (broad s, 1H, NH). ^{13}C NMR (*d6*-DMSO) δ 104.9, 114.1, 125.4, 126.8, 128.5, 130.2, 132.1, 132.5, 149.0, 151.0, 151.1, 155.4. MS (*m/z*) M^+=315 (20.5), 313 (28.8), 271 (68.4), 269 (100).

4.2.9. 6-(2′-Thienyl)-2,4-dihydro-1*H*-thieno[3,2-*d*][1,3]-oxazine-2,4-dione (3i). White solid, mp>250°C, 66%. IR (KBr): 3419, 3106, 1778, 1715, 1460, 986, 845, 692 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 7.02 (s, 1H, H_4), 7.21 (t, $^3J_{HH}$= 3.8 Hz, 1H, $H_{4'}$), 7.68 (d, $^3J_{HH}$=3.8 Hz, 1H, $H_{3'}$), 7.79 (d, $^3J_{HH}$=3.8 Hz, 1H, $H_{5'}$), 12.32 (broad s, 1H, NH). MS (*m/z*) M^+=251 (71.4), 207 (100).

4.2.10. 6-(3′-Thienyl)-2,4-dihydro-1*H*-thieno[3,2-*d*][1,3]-oxazine-2,4-dione (3j). White solid, mp>250°C, 72%. IR (KBr): 3447, 3085, 1792, 1731, 1464, 1005, 852, 701 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 7.13 (s, 1H, H_4), 7.53 (d, $^3J_{HH}$= 3.9 Hz, 1H, $H_{4'}$), 7.69 (d, $^3J_{HH}$=3.9 Hz, 1H, $H_{5'}$), 8.11 (s, 1H, $H_{2'}$), 11.50 (broad s, 1H). MS (*m/z*) M^+=251 (48.4), 207 (100).

4.2.11. 7-Phenyl-2,4-dihydro-1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione (4a). White solid, mp=206°C, 78%. IR (KBr): 3446, 3098, 1788, 1729, 1493, 986, 749, 693 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 7.47 (m, 5H, Har), 8.19 (s, 1H, H_5), 9.95 (broad s, 1H, NH). ^{13}C NMR (*d6*-DMSO) δ 106.9, 128.3, 128.5, 128.7, 132.0, 132.1, 135.7, 148.2, 149.6, 156.3. MS (*m/z*) M^+=245 (39.2), 201 (71.3).

4.2.12. 7-(4′-Flurophenyl)-2,4-dihydro-1*H*-thieno[3,2-*d*]-[1,3]oxazine-2,4-dione (4b). White solid, mp=203°C, 80%. IR (KBr): 3445, 3098, 1786, 1732, 1493, 986, 749, 693 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 7.23 (dt, $^3J_{HH}$=8.3 Hz and $^3J_{HF}$=8.5 Hz, 2H, $H_{3'}$), 7.91 (dd, $^3J_{HH}$=8.4 Hz and $^4J_{HF}$=5.5 Hz, 2H, $H_{2'}$), 8.11 (s, 1H, H_5), 11.75 (broad s, 1H, NH). MS (*m/z*) M^+=263 (40.9), 219 (100).

4.2.13. 7-(4′-Chlorophenyl)-2,4-dihydro-1*H*-thieno[3,2-*d*]-[1,3]oxazine-2,4-dione (4c). Beige solid, mp=245°C, 76%. IR (KBr): 3527, 3077, 1791, 1724, 1470, 986, 791 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 7.44 (d, $^3J_{HH}$=8.4 Hz, 2H, $H_{3'}$), 8.06 (d, $^3J_{HH}$=8.4 Hz, 2H, $H_{2'}$), 8.14 (s, 1H, Har), 10.72 (broad s, 1H, NH). ^{13}C NMR (*d6*-DMSO) δ 105.2, 128.1, 128.2, 128.8, 132.0, 132.5, 133.0, 153.8, 157.7, 159.8. MS (M^+) 281 (21.3), 279 (56), 235 (100).

4.2.14. 7-(4′-Bromophenyl)-2,4-dihydro-1*H*-thieno[3,2-*d*]-[1,3]oxazine-2,4-dione (4d). Pink solid, mp=220°C, 73%. IR (KBr): 3325, 3079, 1774, 1721, 1491, 993, 809, 746 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 7.57 (d, $^3J_{HH}$=7.7 Hz, 2H, $H_{3'}$), 8.02 (d, $^3J_{HH}$=7.7 Hz, 2H, $H_{2'}$), 8.22 (s, 1H, Har), 11.9 (broad s, 1H, NH). ^{13}C NMR (*d6*-DMSO) δ 106.9, 122.7, 128.4, 129.7, 130.6, 131.4, 145.5, 148.1, 152.5, 153.8. MS (*m/z*) M^+=325 (9.5), 323 (10.1), 281 (100), 279 (94.7).

4.2.15. 7-(4′-Methoxyphenyl)-2,4-dihydro-1*H*-thieno-[3,2-*d*][1,3]oxazine-2,4-dione (4e). White solid, mp= 232°C, 75%. IR (KBr): 3323, 3082, 1775, 1719, 1489, 995, 812, 741 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 3.80 (s, 3H, OCH_3), 7.01 (d, $^3J_{HH}$=8.6 Hz, 2H, $H_{3'}$), 7.37 (d, $^3J_{HH}$= 8.6 Hz, 2H, $H_{2'}$), 8.12 (s, 1H, Har), 11.76 (broad s, 1H, NH). ^{13}C NMR (*d6*-DMSO) δ 55.2, 107.0, 114.2, 123.9, 129.9, 131.6, 135.3, 146.3, 148.7, 155.5, 159.4. MS (*m/z*) M^+=275 (71.4), 231 (100).

4.2.16. 7-(3′,4′-Dimethoxyphenyl)-2,4-dihydro-1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione (4f). White solid, mp=246°C, 68%. IR (KBr): 3253, 3078, 1789, 1723, 1526, 990, 812, 692 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 3.79 (2s, 6H, $2OCH_3$), 6.98 (2d, $^3J_{HH}$=9.1 Hz, 2H, $H_{3'}$ and $H_{2'}$), 7.48 (s, 1H, $H_{6'}$), 7.98 (s, 1H, H_5), 11.42 (broad s, 1H, NH). MS (*m/z*) M^+=305 (4.4), 261 (100).

4.2.17. Synthesis of 5-(4′-bromophenyl)-3-[(butoxycarbonyl)amino]thiophen-2-carboxylic acid 5. 1.5 g of **3d** (4.6 mmol) was suspended in 50 ml of *n*-butanol previously treated with 0.24 g (6 mmol) sodium hydride (60%). The mixture was then heated at 116°C for 2 h. After cooling, the solvent was removed under reduced pressure and the residue was taken up in acidic water. The obtained precipitate was washed with water and diethyl ether to give white crystals, mp=124°C, 86%. IR (KBr): 3295, 3024, 2993, 1725, 1580, 1441, 1224, 1092, 1062, 798 cm^{-1}. ^1H NMR (*d6*-DMSO) δ

0.92 (t, $^3J_{HH}$=6.9 Hz, 3H, CH_3), 1.23 (sext., $^3J_{HH}$=6.9 Hz, 2H, CH_2), 1.46 (quint, $^3J_{HH}$=6.9 Hz, 2H, CH_2), 3.87 (t, $^3J_{HH}$=6.9 Hz, 2H, CH_2), 7.21 (s, 1H, H_4), 7.68 (d, $^3J_{HH}$= 8.2 Hz, 2H, $H_{3'}$), 7.82 (d, $^3J_{HH}$=8.2 Hz, 2H, $H_{2'}$), 8.84 (broad s, 1H, NH), 11.51 (broad s, 1H, COOH). MS (*m*/*z*) M^+=399 (30.5), 397 (7.6), 355 (100), 353 (12.8).

4.2.18. Synthesis of 3-[(benzylaminocarbonyl)amino]-4-phenyl-thiophen-2-carboxylic acid 6. 1.5 g of **4a** (4.6 mmol) was suspended in 50 ml of THF. 0.66 ml (6 mmol) of benzylamine was added and the mixture was then refluxed for 2 h. After cooling, the solvent was removed under reduced pressure and the residue was taken up in water. The obtained precipitate after triturating was washed with water and petroleum ether to give **6** (white crystals), mp=178°C, 83%. IR (KBr): 3317, 3024, 2924, 1672, 1652, 1581, 1445, 1220, 1085, 986, 697 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 4.13 (s, 2H, CH_2), 7.24 (m, 11H, Har), 7.83 (s, 1H, H_5), 8.44 (broad s, 1H, NH), 13.13 (broad s, 1H, NH). ^{13}C NMR (*d6*-DMSO) δ 42.6, 119.7, 126.5, 126.8, 126.9, 128.1, 128.3, 128.8, 136.1, 139.7, 140.3, 141.4, 154.8, 163.6. MS (*m*/*z*) M^+=352 (30.1), 308 (100).

4.3. General procedures for the synthesis of products 7a–j and 8a–j

1 mmol of corresponding anhydride **3** or **4** was suspended in 10 ml of water. 2.2 mmol of amine was then added at room temperature. The mixture was then stirred for 1 h. 3 ml of a 37% HCl solution was added. Obtained precipitate was washed with water and petroleum ether to give **7a–j** and **8a–j** (white solid).

4.3.1. 3-[(*N*-Benzylanilino)carbonylamino]-5-(4′-chlorophenyl)thiophen-2-carboxylic acid (7a). White solid, mp=180°C, 90%. IR (KBr): 3329, 3061, 2948, 1672, 1654, 1556, 1439, 1295, 1090, 938, 787 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 4.40 (s, 2H, CH_2), 7.31 (m, 14H, Har), 8.25 (s, 1H, H_4), 11.88 (broad s, 1H, NH), 12.53 (broad s, 1H, COOH).

4.3.2. 5-(4′-Chlorophenyl)-3-[(cyclopentylamino)carbonylamino]-thiophen-2-carboxylic acid (7b). White solid, mp=214°C, 92%. IR (KBr): 3305, 3041, 2927, 1663, 1641, 1549, 1457, 1267, 1092, 821 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 1.57 (m, 8H, $4CH_2$), 3.61 (quint, $^3J_{HH}$=8.2 Hz, 1H, CH), 6.96 (broad s, 1H, NH), 7.38 (2d, $^3J_{HH}$=7.4 Hz, 4H, $H_{2'}$ and $H_{3'}$), 7.78 (s, 1H, H_4), 8.33 (broad s, 1H, NH), 12.51 (broad s, 1H, COOH).

4.3.3. 5-(4′-Chlorophenyl)-3-[(phenylethylamino)carbonylamino]-thiophen-2-carboxylic acid (7c). White solid, mp=206°C, 89%. IR (KBr): 3311, 3021, 2961, 1667, 1640, 1547, 1458, 1282, 1092, 820 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 2.53 (t, $^3J_{HH}$=7.3 Hz, 2H, CH_2), 3.09 (t, $^3J_{HH}$=7.3 Hz, 2H, CH_2), 6.92 (broad s, 1H, NH), 7.36 (m, 5H, Har), 7.39 (2d, $^3J_{HH}$=7.4 Hz, 4H, $H_{2'}$ and $H_{3'}$), 7.78 (s, 1H, NH), 8.37 (broad s, 1H, NH), 12.16 (broad s, 1H, COOH).

4.3.4. 3-[(2′,5′-Dichloroanilino)carbonylamino]-5-(4′-chlorophenyl)-thiophen-2-carboxylic acid (7d). White solid, mp=220°C, 88%. IR (KBr): 3322, 3017, 2962, 1674, 1644, 1557, 1451, 1291, 1088, 832 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 5.63 (broad s, 1H, NH), 6.52 (d, $^3J_{HH}$= 8.3 Hz, 1H, $H_{3''}$), 6.79 (s, 1H, $H_{6''}$), 7.18 (d, $^3J_{HH}$=8.3 Hz, 1H, $H_{4''}$), 7.45 (d, $^3J_{HH}$=8.0 Hz, 2H, $H_{3'}$), 7.53 (d, $^3J_{HH}$= 8.0 Hz, 2H, $H_{2'}$), 8.23 (s, 1H, H_4), 11.86 (broad s, 1H, NH), 12.48 (broad s, 1H, COOH).

4.3.5. 5-(4′-Chlorophenyl)-3-[(4′-methylpiperidino)carbonylamino]-thiophen-2-carboxylic acid (7e). White solid, mp=196°C, 93%. IR (KBr): 3320, 3022, 2984, 1670, 1640, 1561, 1471, 1289, 1088, 831 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 0.89 (m, 7H, $2CH_2$ and CH_3), 1.53 (t, $^3J_{HH}$=10.7 Hz, 4H, $2CH_2$), 2.73 (quint, $^3J_{HH}$=10.7 Hz, 1H, CH), 7.42 (2d, $^3J_{HH}$=8.2 Hz, 4H, $H_{2'}$ and $H_{3'}$), 7.81 (s, 1H, H_4), 8.38 (broad s, 1H, NH), 11.95 (broad s, 1H, NH).

4.3.6. 3-[(Butylamino)carbonylamino]-5-(4′-chlorophenyl)-thiophen-2-carboxylic acid (7f). White solid, mp=192°C, 89%. IR (KBr): 3420, 3017, 2978, 1663, 1636, 1575, 1457, 1229, 1101, 830 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 0.80 (t, $^3J_{HH}$=7.1 Hz, 3H, CH_3), 1.19 (m, 4H, $2CH_2$), 2.84 (t, $^3J_{HH}$=7.1 Hz, 2H, CH_2), 6.88 (broad s, 1H, NH), 7.38 (d, $^3J_{HH}$=8.2 Hz, 2H, $H_{3'}$), 7.41 (d, $^3J_{HH}$=8.2 Hz, 2H, CH_2), 7.78 (s, 1H, H_4), 8.33 (broad s, 1H, NH), 10.96 (broad s, 1H, COOH).

4.3.7. 5-(4′-Chlorophenyl)-3-[(diisopropylamino) carbonylamino]-thiophen-2-carboxylic acid (7g). White solid, mp=220°C, 94%. IR (KBr): 3331, 3011, 2972, 1666, 1636, 1576, 1458, 1262, 1091, 818 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 1.20 (d, $^3J_{HH}$=6.4 Hz, 12H, $4CH_3$), 3.92 (sept., $^3J_{HH}$= 6.4 Hz, 2H, 2CH), 7.49 (d, $^3J_{HH}$=8.2 Hz, 2H, $H_{3'}$), 7.66 (d, $^3J_{HH}$=8.2 Hz, 2H, $H_{2'}$), 8.21 (s, 1H, H_4), 8.55 (broad s, 1H, NH), 11.38 (broad s, 1H, COOH).

4.3.8. 5-(4′-Chlorophenyl)-3-[(diethylamino) carbonylamino]-thiophen-2-carboxylic acid (7h). White solid, mp=194°C, 95%. IR (KBr): 3332, 3010, 2972, 1667, 1636, 1577, 1457, 1282, 1092, 818 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 1.23 (t, $^3J_{HH}$=6.4 Hz, 6H, $2CH_3$), 3.22 (q, $^3J_{HH}$=6.4 Hz, 4H, $2CH_2$), 7.51 (d, $^3J_{HH}$=8.2 Hz, 2H, $H_{3'}$), 7.65 (d, $^3J_{HH}$=8.2 Hz, 2H, $H_{2'}$), 8.01 (s, 1H, H_4), 9.32 (broad s, 1H, NH), 10.98 (broad s, 1H, COOH).

4.3.9. 5-(4′-Chlorophenyl)-3-[(morpholino) carbonylamino]-thiophen-2-carboxylic acid (7i). White solid, mp=206°C, 88%. IR (KBr): 3304, 3019, 2952, 1669, 1641, 1551, 1459, 1283, 1091, 821 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 3.34 (t, $^3J_{HH}$=4.2 Hz, 4H, $2CH_2$), 3.52 (t, $^3J_{HH}$= 4.2 Hz, 4H, $2CH_2$), 7.45 (d, $^3J_{HH}$=8.2 Hz, 2H, $H_{3'}$), 7.46 (d, $^3J_{HH}$=8.2 Hz, 2H, $H_{3'}$), 7.86 (s, 1H, H_4), 8.39 (broad s, 1H, NH), 13.18 (broad s, 1H, COOH).

4.3.10. 3-[(2′-Chloroanilino)carbonylamino]-5-(4′-chlorophenyl)-thiophen-2-carboxylic acid (7j). White solid, mp=190°C, 84%. IR (KBr): 3322, 3009, 2962, 1674, 1643, 1556, 1451, 1291, 1226, 832 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 5.28 (broad s, 1H, NH), 6.51 (t, $^3J_{HH}$= 9.4 Hz, 1H, $H_{5''}$), 6.76 (d, $^3J_{HH}$=9.4 Hz, 1H, $H_{6''}$), 7.00 (t, $^3J_{HH}$=9.4 Hz, 1H, $H_{4''}$), 7.16 (d, $^3J_{HH}$=9.4 Hz, 1H, $H_{3''}$), 7.51 (d, $^3J_{HH}$=8.2 Hz, 2H, $H_{3'}$), 7.56 (d, $^3J_{HH}$=8.2 Hz, 2H, $H_{2'}$), 8.23 (s, 1H, H_4), 8.74 (broad s, 1H, NH), 11.85 (broad s, 1H, NH).

4.3.11. 5-Phenyl-3-[(propylamino)carbonylamino]-thiophen-2-carboxylic acid (8a). White solid, mp=194°C, 93%. IR (KBr): 3314, 3062, 2962, 1671, 1644, 1557, 1460, 1286, 1235, 683 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 0.85 (t, $^3J_{HH}$=7.1 Hz, 3H, CH_3), 1.42 (sext., $^3J_{HH}$=7.1 Hz, 2H, CH_2), 3.02 (t, $^3J_{HH}$=7.1 Hz, 2H; CH_2), 7.34 (broad s, 1H, NH), 7.6 (m, 5H, Har), 8.3 (s, 1H, H_4), 9.3 (broad s, 1H, NH), 13.1 (broad s, 1H, COOH).

4.3.12. 5-(4′-Fluorophenyl)-3-[(propylamino)carbonylamino]-thiophen-2-carboxylic acid (8b). White solid, mp=204°C, 95%. IR (KBr): 3315, 3065, 2962, 1675, 1641, 1551, 1460, 1286, 1235, 681 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 0.87 (t, $^3J_{HH}$=7.1 Hz, 3H, CH_3), 1.44 (sext., $^3J_{HH}$=7.1 Hz, 2H, CH_2), 3.03 (t, $^3J_{HH}$=7.1 Hz, 2H, CH_2), 7.35 (t, $^3J_{HH}$=6.5 Hz, 2H, $H_{3'}$), 7.40 (broad s, 1H, NH), 7.67 (d, $^3J_{HH}$=6.5 Hz, 2H, $H_{2'}$), 8.21 (s, 1H, H_4), 9.38 (broad s, 1H, NH), 13.0 (broad s, 1H, NH).

4.3.13. 5-(4′-Chlorophenyl)-3-[(propylamino)carbonylamino]-thiophen-2-carboxylic acid (8c). White solid, mp=218°C, 93%. IR (KBr): 3311, 3026, 2963, 1668, 1642, 1552, 1460, 1284, 1235, 820 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 0.89 (t, $^3J_{HH}$=7.1 Hz, 3H, CH_3), 1.47 (sext., $^3J_{HH}$=7.1 Hz, 2H, CH_2), 3.08 (t, $^3J_{HH}$=7.1 Hz, 2H, CH_2), 7.51 (d, $^3J_{HH}$=7.9 Hz, 2H, $H_{3'}$), 7.61 (broad s, 1H, NH), 7.68 (d, $^3J_{HH}$=7.9 Hz, 2H, $H_{2'}$), 8.24 (s, 1H, H_4), 9.62 (broad s, 1H, NH), 12.38 (broad s, 1H, COOH).

4.3.14. 5-(4′-Bromophenyl)-3-[(propylamino)carbonylamino]-thiophen-2-carboxylic acid (8d). White solid, mp=210°C, 94%. IR (KBr): 3305, 3026, 2966, 1664, 1644, 1555, 1456, 1275, 1019, 811 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 0.87 (t, $^3J_{HH}$=7.0 Hz, 3H, CH_3), 1.43 (sext., $^3J_{HH}$=7.0 Hz, 2H, CH_2), 3.04 (t, $^3J_{HH}$=7.1 Hz, 2H, CH_2), 7.46 (d, $^3J_{HH}$=7.9 Hz, 2H, $H_{3'}$), 7.49 (broad s, 1H, NH), 7.56 (d, $^3J_{HH}$=7.9 Hz, 2H, $H_{2'}$), 8.29 (s, 1H, H_4), 9.31 (broad s, 1H, NH), 13.14 (broad s, 1H, COOH).

4.3.15. 5-(4′-Methylphenyl)-3-[(propylamino)carbonylamino]-thiophen-2-carboxylic acid (8e). White solid, mp=194°C, 95%. IR (KBr): 3305, 3026, 2966, 1666, 1642, 1558, 1456, 1288, 1019, 813 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 0.87 (t, $^3J_{HH}$=7.0 Hz, 3H, CH_3), 1.44 (sext., $^3J_{HH}$=7.0 Hz, 2H, CH_2), 2.32 (s, 3H, CH_3), 3.04 (t, $^3J_{HH}$=7.1 Hz, 2H, CH_2), 7.25 (d, $^3J_{HH}$=7.8 Hz, 2H, $H_{3'}$), 7.54 (broad s, 1H, NH), 7.66 (d, $^3J_{HH}$=7.8 Hz, 2H, $H_{2'}$), 8.21 (s, 1H, H_4), 9.33 (broad s, 1H, NH), 12.5 (broad s, 1H, COOH).

4.3.16. 5-(4′-Methoxyphenyl)-3-[(propylamino)carbonylamino]-thiophen-2-carboxylic acid (8f). White solid, mp=200°C, 91%. IR (KBr): 3305, 3027, 2966, 1664, 1646, 1558, 1456, 1286, 1275, 1019, 811 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 0.84 (t, $^3J_{HH}$=7.0 Hz, 3H, CH_3), 1.41 (sext., $^3J_{HH}$=7.0 Hz, 2H, CH_2), 3.00 (t, $^3J_{HH}$=7.1 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 6.97 (d, $^3J_{HH}$=7.8 Hz, 2H, $H_{3'}$), 7.53 (broad s, 1H, NH), 7.58 (d, $^3J_{HH}$=7.8 Hz, 2H, $H_{2'}$), 8.10 (s, 1H, H_4), 9.45 (broad s, 1H, NH), 12.89 (broad s, 1H, COOH).

4.3.17. 5-(3′,4′-Dimethoxyphenyl)-3-[(propylamino)carbonylamino]-thiophen-2-carboxylic acid (8g). White solid, mp=200°C, 93%. IR (KBr): 3305, 3024, 2966, 1665, 1639, 1555, 1456, 1288, 1019, 811 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 0.89 (t, $^3J_{HH}$=6.5 Hz, 3H, CH_3), 1.47 (sext., $^3J_{HH}$=6.5 Hz, 2H, CH_2), 3.03 (t, $^3J_{HH}$=6.5 Hz, 2H, CH_2), 3.83 (2s, 6H, $2OCH_3$), 7.01 (d, $^3J_{HH}$=8.3 Hz, 1H, $H_{3'}$), 7.13 (s, 1H, H_6), 7.20 (d, $^3J_{HH}$=8.3 Hz, 1H, $H_{2'}$), 7.67 (broad s, 1H, NH), 8.16 (s, 1H, H_4), 9.31 (broad s, 1H, NH), 13.00 (broad s, 1H, COOH).

4.3.18. 4-Phenyl-3-[(propylamino)carbonylamino]-thiophen-2-carboxylic acid (8h). White solid, mp=168°C, 95%. IR (KBr): 3329, 3025, 2963, 1669, 1651, 1557, 1447, 1291, 1229, 751 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 0.76 (t, $^3J_{HH}$=6.5 Hz, 3H, CH_3), 1.26 (sext., $^3J_{HH}$=6.5 Hz, 2H, CH_2), 2.81 (t, $^3J_{HH}$=6.5 Hz, 2H, CH_2), 6.82 (broad s, 1H, NH), 7.26 (m, 5H, Har), 7.72 (s, 1H, H_5), 8.36 (broad s, 1H, NH), 13.08 (broad s, 1H, COOH).

4.3.19. 4-(4′-Fluorophenyl)-3-[(propylamino)carbonylamino]-thiophen-2-carboxylic acid (8i). White solid, mp=168°C, 95%. IR (KBr): 3323, 3021, 2968, 1662, 1647, 1565, 1447, 1287, 1229, 1011, 751 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 0.77 (t, $^3J_{HH}$=6.5 Hz, 3H, CH_3), 1.23 (sext., $^3J_{HH}$=6.5 Hz, 2H, CH_2), 2.80 (t, $^3J_{HH}$=6.5 Hz, 2H, CH_2), 6.87 (broad s, 1H, NH), 7.14 (t, $^3J_{HH}$=8.2 Hz, 2H, $H_{3'}$), 7.41 (d, $^3J_{HH}$=8.2 Hz, 2H, $H_{2'}$), 7.76 (s, 1H, H_5), 8.29 (broad s, 1H, NH), 13.15 (broad s, 1H, COOH).

4.3.20. 4-(4′-Bromophenyl)-3-[(propylamino)carbonylamino]-thiophen-2-carboxylic acid (8j). White solid, mp=160°C, 92%. IR (KBr): 3315, 3089, 2962, 1674, 1652, 1570, 1444, 1294, 1229, 1010, 790 cm^{-1}. ^1H NMR (*d6*-DMSO) δ 0.75 (t, $^3J_{HH}$=6.5 Hz, 3H, CH_3), 1.25 (sext., $^3J_{HH}$=6.5 Hz, 2H, CH_2), 2.72 (t, $^3J_{HH}$=6.5 Hz, 2H, CH_2), 6.94 (broad s, 1H, NH), 7.34 (d, $^3J_{HH}$=8.2 Hz, 2H, $H_{3'}$), 7.50 (d, $^3J_{HH}$=8.2 Hz, 2H, $H_{2'}$), 7.88 (s, 1H, H_5), 8.36 (broad s, 1H, NH), 13.13 (broad s, 1H, COOH).

Acknowledgements

The authors thank the Conseil Regional de Basse-Normandie the PUNCHOrga (Pôle Universitaire Normand de Chimie Hétérocyclique et Organique) and FEDER (Fonds Européens de Développement Economique Régional) for their financial support.

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