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Original article

Design and synthesis of naphthalenic derivatives as new ligands at the melatonin binding site MT_3

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ABSTRACT

Naphthalenic analogs of MCA-NAT (5-methoxycarbonylamino-*N*-acetyltryptamine) have been synthesized and evaluated as melatonin receptor ligands. Introduction of a methoxycarbonylamino substituent at the C-7 position of the naphthalenic nucleus yields MT_3 selective ligands. This selectivity can be modulated with suitable variations of the C-7 position and the acyl group on the C-1 side chain. We identified new series of compounds with affinity for the MT_3 binding site in the nanomolar range, and singled out a selective ligand, (*N*-[2-(7-methylsulfamoyl-naphth-1-yl)ethyl]acetamide (**17**), with a Ki of 4.9 nM and selectivity of 1024 and 2040 versus MT_1 and MT_2 receptors respectively.

1. Introduction

N-acetyl-5-methoxytryptamine (melatonin) is a neurohormone synthesized and secreted following a circadian rhythm with the higher levels being released at night [1] by the pineal gland. The regulation of its production is achieved by a photoperiodic mechanism and therefore, melatonin plays an important part in the adaptation of mammalian circadian rhythms and reproduction functions to the environment. It is also implicated in several physiopathological states. These biological effects have hinted to a possible therapeutic use of melatonin in some disorders [2–5]. Melatonin binds to two kinds of sites. High affinity binding sites belong to the G-Protein Coupled Receptors (GPCR) super family and have been divided into MT_1 and MT_2 [6,7]. The low affinity binding site, MT_3 [8,9], which has been identified as the quinone reductase 2 (QR2 EC 1.6.99.2) [10]. Although it is closely related to the detoxifying enzyme quinone reductase 1, its exact biological relevance in melatonin's effects is still uncertain [11]. Nonetheless, MT_3 has shown to be involved in acute inflammatory responses in the rat [12] and in the regulation of intraocular pressure in the rabbit [13]. It has proved to be a target worthy of more in depth investigations, leading to ligand-based *in silico* [14,15] and crystallographic studies [16,17].

An accurate characterization of MT_3 mediated functions in native tissues can only be made using specific ligands. Unfortunately, only a few selective ligands have been reported to date (Chart 1). Among them, 5-methoxycarbonylamino-*N*-acetyltryptamine (MCA-NAT) has been the first to show a selectivity toward this subtype and has a good affinity (IC_{50} = 2.7 nM) [18]. Prazosine, an α_1-adrenoceptor antagonist, also acts as a MT_3 selective ligand (IC_{50} = 7.8 nM) [19]. Nitroindole derivative (S27533) [20] (Ki = 0.3 nM), and DMHMIO (8-Hydroxy-2,3-dimethoxy-5-methyl-5H-indeno[1,2-b]indol-10-one) [21] (Ki = 0.19 nM) have been described. Recently, we have published novel benzofuranic derivatives (MCA-B) as MT_3 selective ligands (Ki = 24 nM) [22]. We have further studied the MT_3 binding sites requirements by noting that MCA-NAT includes a methoxycarbonylamino group in the 5-position instead of the melatonin's methoxy. We replaced the indolic cycle of MCA-NAT with naphthalene (**4**, S26553). Furthermore, in the hope of better modulating the fit to the MT_3 binding site, we replaced the

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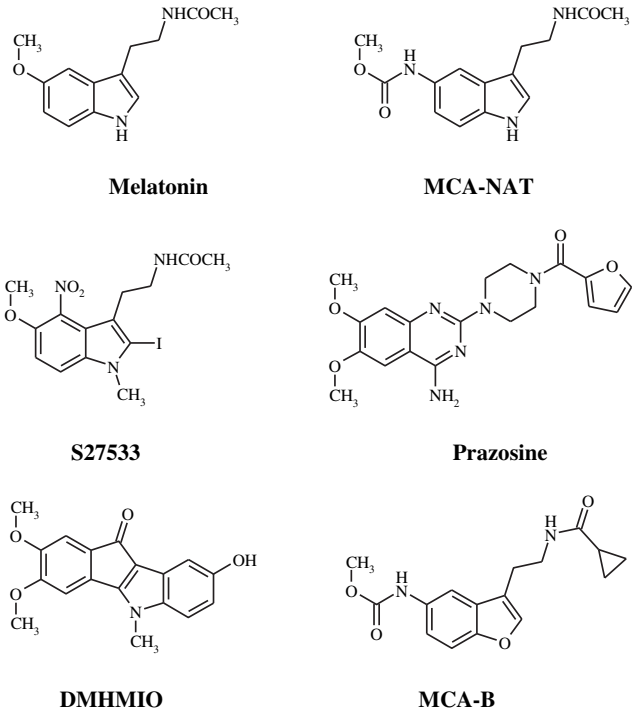


Chart 1. Chemical Structures of Melatonin and MT_3 Derivatives.

methoxycarbonylamino group of **4**, with sulfite, sulfone, sulfoxide and sulfonamide functions. In order to explore the role of the *N*-acyl side chain on the binding affinity and the selectivity, we replaced the methyl of the acetamido function with furyl group (Table 1).

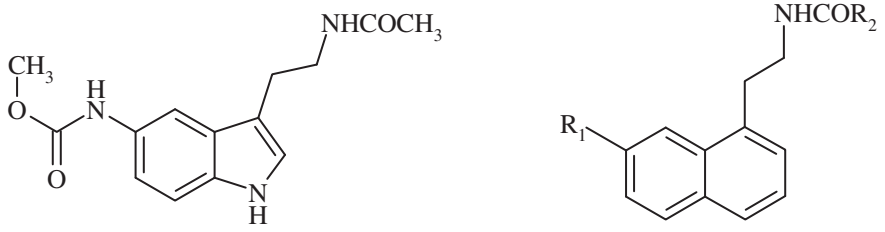
For all these compounds, the synthesis, the binding data for the human MT_1 and MT_2 receptors and MT_3 binding site are reported.

2. Chemistry

Compounds listed in Table 1 were synthesized according to Schemes 1–5. The synthesis of carbamate **4** (Scheme 1) was elaborated in four steps from the starting material, i.e. *N*-[2-(7-hydroxynaphth-1-yl)ethyl]acetamide, which synthesis is described previously [23]. The hydroxyl group was activated by trifluoromethanesulfonic anhydride in the presence of triethylamine in dichloromethane to lead in the triflate **1** with a 65% yield. The replacement of the triflate substituent was accomplished in a weak yield (40%) by reacting compound **1** with 4-methoxybenzylamine, in a sealed tube in microwave (10 min at 100 W), in the presence of palladium acetate and cesium carbonate in dry *N,N*-dimethylformamide. Then the compound **2** was debenzylated under hydrogene atmospheric pressure in presence of palladium on charcoal catalyst to obtain the crude coumpound **3**, which was engaged in the next step without further purification. Finally the carbamate **4** was obtained from **3** by reaction of methyl chloroformate in a biphasic mixture in the presence of potassium carbonate.

The synthesis of the methylsulfide (**11**) was conceived in four steps from 7-methylsulfanyl-3,4-dihydro-2*H*-naphthalen-1-one (**7**), which was obtained from thioanisole by adapted and optimizated methods described by Cagniant [24] and Buu-Hoi [25] (Scheme 2). The naphthyl acetonitrile derivative **9** was prepared from compound **7** with good yields by a Wadsworth–Emmons's reaction using diethyl cyanomethyl phosphonate followed by heating the intermediate acrylonitrile **8** at fusion with sulfur. The amino compound **10** was obtained by reduction with borane-THF complex and condensated with various acetyl chlorides to give compound **11** with moderate yields.

Table 1
MT_1, MT_2 and MT_3 binding affinities of naphthalenic compounds.



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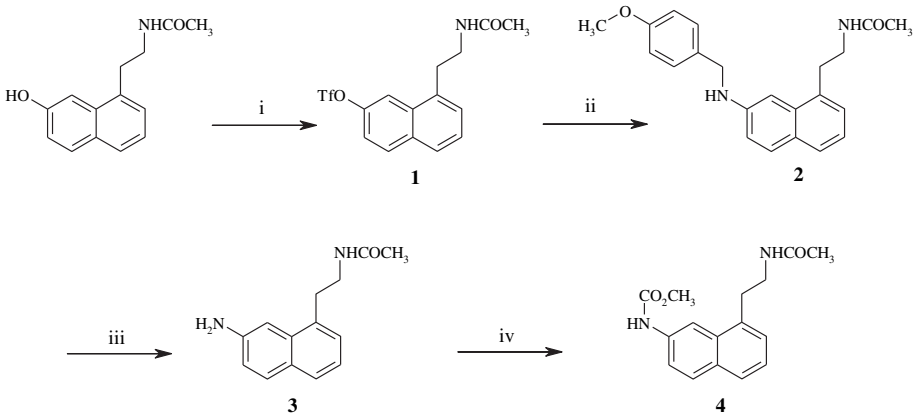
Compd.	R_1	R_2	IC_{50} (nM) MT_1	IC_{50} (nM) MT_2	IC_{50} (nM) MT_3	S MT_1/MT_3 MT_2/MT_3
Melatonin	–	–	0.20 ± 0.03	0.53 ± 0.06	64.6 ± 0.9	1/323 1/122
MCA-NAT	–	–	1000 ± 44	4000 ± 53	58.0 ± 0.1	17 69
4 (S26553)	$NHCO_2CH_3$	CH_3	85.4 ± 3	26.3 ± 11	0.39 ± 0.1	219 67
11 (S24203)	SCH_3	CH_3	0.875 ± 0.07	0.955 ± 0.04	18.0 ± 1	1/20 1/19
12 (S26805)	$SOCH_3$	CH_3	77.6 ± 7	97.0 ± 16	37.0 ± 6	2 3
13 (S26716)	SO_2CH_3	CH_3	477 ± 13	879 ± 272	21 ± 4	23 42
16 (S26799)	SO_2NH_2	CH_3	310 ± 50	371 ± 31.5	32 ± 3	10 12
17 (S26695)	SO_2NHCH_3	CH_3	5000 ± 1730	>10 000	4.9 ± 0.3	1020 >2040
19 (S27784)	SO_2NHCH_3	furyl	2610 ± 45	6840 ± 130	9.1 ± 0.2	287 752

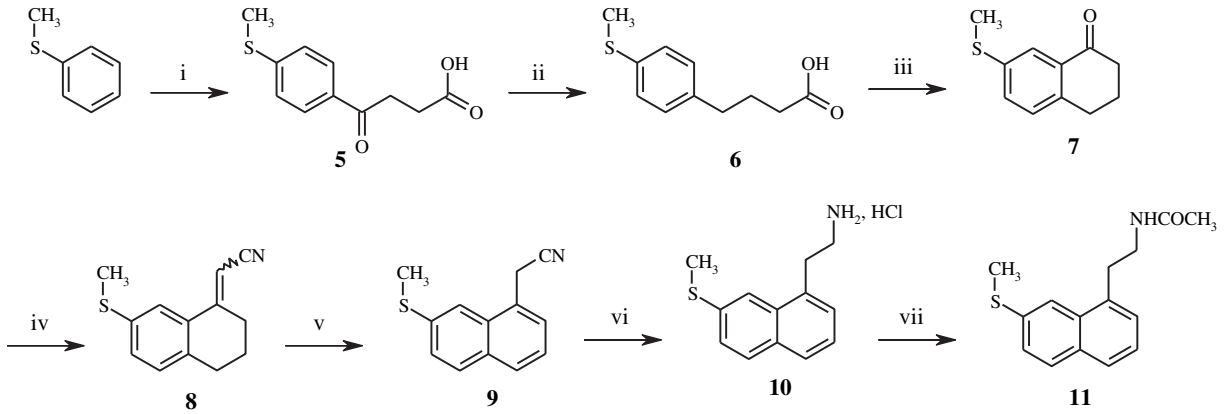


Scheme 1. Synthesis of carbamate **4**. *Reagents* : (i) $(TfO)_2O$, CH_2Cl_2, Et_3N, −20 °C, 3 h (65%); (ii) $(4\text{-}OCH_3)C_6H_4CH_2NH_2$, $Pd(AcO)_2$, Xantphos, Cs_2CO_3, DMF, microwave, 100 W, 10 min (40%); (iii) CH_3OH, Pd/C, r.t., 12 h (62%); (iv) CH_3CO_2Cl, K_2CO_3, EtOAc/H_2O, 1 h (68%).

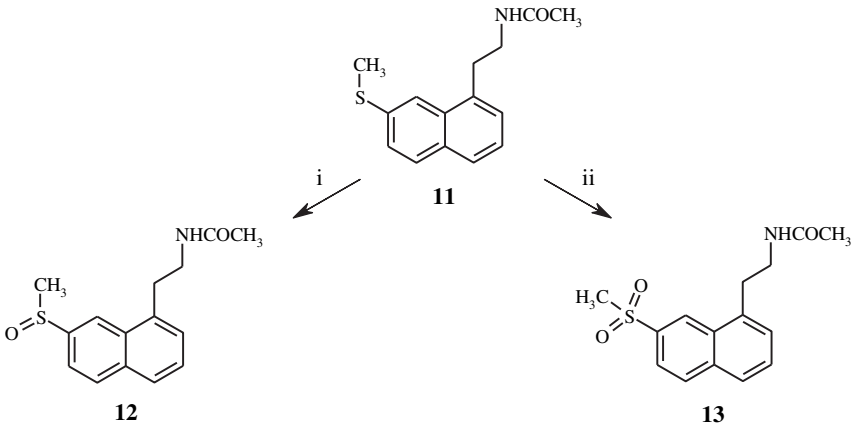
Oxidation using 1 or 3 equivalents of *m*-CPBA of the sulfide compound **11** led to the sulfoxide derivative **12** and the sulfone derivative **13** respectively with good yields (Scheme 3). Sulfonamides **16-17** were prepared in three steps from the starting material *N*-[2-(7-hydroxy-naphth-1-yl)ethyl]acetamide (Scheme 4). The substitution of the hydroxy group with benzylthiol in the presence of trifluoromethanesulfonic acid at 60 °C [26] readily took place to give sulfide compound **14**. Sulfonyl chloride **15** was synthesized in one-step from benzylsulfide **14** by crushing and grinding it with a pestle in presence of a mixture of HCl-treated silica gel and freshly prepared iodosobenzene with a 54% yield [27]. Reaction of **15** with a 28% aqueous ammoniac or methylamine in presence of triethylamine gave the corresponding sulfonamides **16-17** respectively with very good yields. The derivative **19** (Scheme 5) was prepared with good yields by heating compound **16** with 6 M HCl aqueous solution followed by acylating the intermediate amine **18** with 2-furoyl chloride in the presence of triethylamine in dichloromethane.

3. Results and discussion

Although MCA-NAT has the same affinity for MT_3 as melatonin, it displays a modest but fairly interesting selectivity for this subtype as its MT_1 and MT_2 affinities are about 4000-fold worse than those of melatonin. This is a clear clue about the steric tolerance of the MT_3 binding site, which is able to accommodate larger moieties in position 5 than the more restricted GPCR-type binding sites. Previous studies of our group have showed that melatoninergic affinity was retained when the indolic cycle of melatonin was replaced with naphthalene. Our first guess to overcome this lack of selectivity was to reproduce the same indol-naphthalen isostery with MCA-NAT, leading to compound **4**. This compound has noticeably lower affinities for the GPCRs, while it has a subnanomolar affinity for MT_3, endowing it with fairly good selectivities of respectively more than 219 and 67 against MT_1 and MT_2. These results are similar to those we have already described for benzofuranic compounds [22]. Another possibility was to take advantage of the larger steric tolerance of MT_3 at the 5 position by replacing the methoxy group with larger moieties. The first function we tried was a sulfite (**11**). This compound yields affinities for the GPCR sites that are nearly identical to those of melatonin itself but a 4-fold better affinity for MT_3, although it is not sufficient to give it any selectivity for this subtype. A first oxidation step yields the sulfonyl **12**. This slightly larger function brings a 100-fold drop in GPCR binding, but also a 2-fold worse affinity for MT_3, thus giving it a mediocre 2 to 3 selectivity for this subtype. A further oxidation affords the sulfoxide **13**, which loses again a factor 10 in its GPCR binding sites affinities but keeps an MT_3 affinity similar to that of the sulfite. The net result was selectivity close to that of MCA-NAT. A second series of compounds was derived from the sulfoxide, with



Scheme 2. Synthesis of compound **11**. *Reagents* : (i) $AlCl_3$, succinic anhydride, $C_2H_2Cl_4$, 60 °C, 3 h (67%); (ii) Et_3SiH, TFA, 0 °C, 17 h (94%); (iii) PPA, 70 °C, 2 h (66%); (iv) NaH, $(EtO)_2P(O)CH_2CN$, 0 °C then r.t., 3 h (89%); (v) S, >230 °C (fusion), 10 h (64%); (vi) BH_3-THF, THF, N_2, reflux, 5 h, then HCl_{gas}-saturated Et_2O (75%); (vii) : CH_3COCl, K_2CO_3, CH_2Cl_2/H_2O, 30 min (57%).



Scheme 3. Synthesis of compounds **12** and **13**. *Reagents* : (i) *m*-CPBA (1 eq), CH_2Cl_2, 2 h (88%); (ii) *m*-CPBA (3 eq), CH_2Cl_2, 2 h (63%).

the introduction of a sulfonamide group. Compound **16** is the direct analog of **13**. While the MT_1 affinity of this last compound was conserved, its MT_2 affinity is nearly 2-fold better and its MT_3 affinity one third worse, therefore lowering drastically its selectivity. Adding a methyl to the sulfonamide in order to increase its volume leads to **17** and nearly abolishes high affinity sites binding, but in the meantime improves the MT_3 affinity to a great extend, with a 10-fold better value than MCA-NAT, yielding selectivity values of 1020 for MT_1 and up to 2040 for MT_2. This makes **17** the most selective compound of this series and an interesting pharmacological tool for the elucidation of MT_3 biological relevance. Taking into account the structure of Prazosine, we have introduced a 2-furyl on the amidoethyl chain of **17**, affording compound **19**. However, compared to its parent, this leads to 2-fold better affinity for MT_1 and a slight improvement of MT_2 affinity as well, but also a nearly 2-fold loss in MT_3 affinity. Although **19** is still about 300-fold more selective for MT_3 against MT_1 and 750-fold against MT_2, it is far from being as selective as its methylated counterpart.

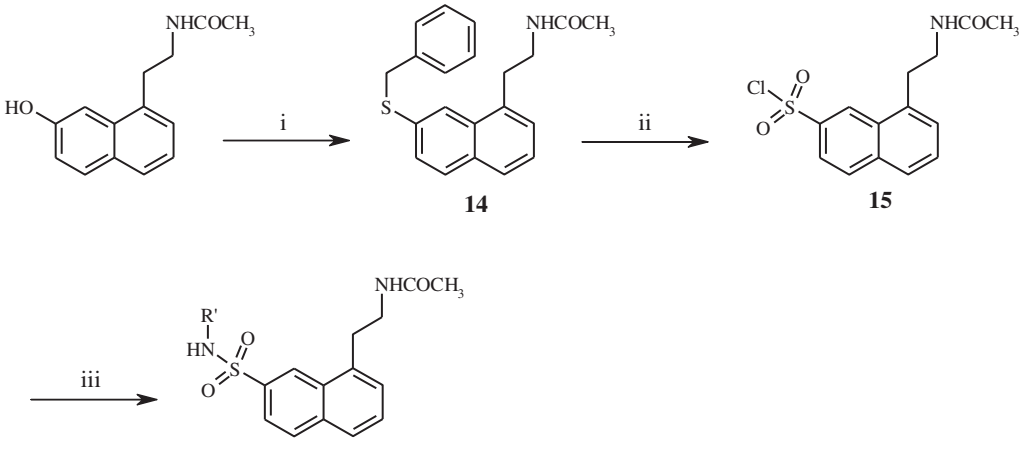
4. Conclusions

Replacement of the indolic cycle of the MCA-NAT by a naphthalenic nucleus led to new series of MT_3 ligands. Introduction of a methoxycarbonylamino group in the C-7 position of the naphthalene allows access to MT_3 selective ligands. The most selective compounds **17** and **19**, obtained by substitution of the methoxycarbonylamino group by a sulfonamide substituents, show selectivity values upon MT_3 noticeably higher than that of MCA-NAT, respectively of 1020 for MT_1 and up to 2040 for MT_2 and 300 for MT_1 and 750 MT_2.

5. Experimental

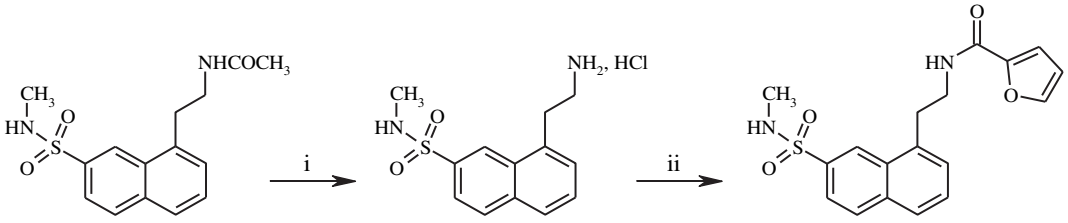
5.1. Chemistry

Melting points were determined on a Büchi SMP-20 capillary apparatus and are uncorrected. IR spectra were recorded on



Compound	R'
16	H
17	CH_3

Scheme 4. Synthesis of compounds **16** and **17**. *Reagents* : (i) $C_6H_5CH_2SH$, CF_3SO_3H, N_2, 60 °C, 2–3 h (48%); (ii) C_6H_5IO, HCl–SiO_2, 10 min (54%); (iii) $R'NH_2$, Et_3N, CH_2Cl_2, 2 h (87–95%).



16 18 19

Scheme 5. Synthesis of the compound **19**. *Reagents* : (i) 6 M HCl, reflux, 16 h (71%); (ii) 2-furoyl chloride, Et_3N, CH_2Cl_2, 3 h (63%).

a Vector 22 Bruker spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on an AC 300 Bruker spectrometer. Chemical shifts are reported in δ units (parts per million) relative to TMS. Mass spectra were performed on a Finnigan MAT SSQ 710 Advantage spectrometer and were recorded in the APCI positive mode. Elemental analyses for tested compounds were performed by CNRS Laboratories (Vernaison, France). Obtained results were within ±0.4% of the theoretical values.

5.2. *N-[2-(7-trifluoromethansulfonyl-naphth-1-yl)ethyl] acetamide (**1**)*

To a stirred solution of *N*-[2-(7-hydroxy-napht-1-yl)ethyl]acetamide (7.5 g, 33 mmol) in dichloromethane (200 mL) was added triethylamine (13.8 mL, 100 mmol). The mixture was cooled to −20 °C under nitrogen atmosphere and trifluoromethanesulfonic anhydride (6 mL, 35 mmol) was slowly added. The reaction mixture was stirred for 5 h and poured into ice-cold water and then extracted with ethyl acetate. The organic layer was washed successively with water, an aqueous solution of sodium hydroxide (1 M) and water, and then dried over $MgSO_4$. The solvent was removed and the oily residue was purified by column chromatography over silica gel with acetone/cyclohexane (3/7) to give **1** as a white solid; Yield 65%, mp 82–83 °C, Recrystallized from toluene/cyclohexane. IR (KBr), cm^{-1}: 3300 (NH), 1620 (C=O). ^1H NMR (DMSO-d_6): δ_H 1.81 (s, 3H, CH_3), 3.18 (t, 2H, J = 7.7 Hz, CH_2-a), 3.32 (m, 2H, CH_2-b), 7.40–7.60 (m, 3H, H-2, 3 and 6), 7.93 (dd, 1H, J = 8.1, 2.2 Hz, H-4), 8.06 (br s, 1H, NH), 8.15 (d, 1H, J = 8.1 Hz, H-5), 8.31 (d, 1H, J = 2.2 Hz, H-8). MS: m/z = 362 $[M + H]^+$.

5.3. *N-(2-{7-[(4-Methoxybenzyl)amino]naphth-1-yl}ethyl)acetamide hydrochloride (**2**)*

Compound **1** (1 g, 2.8 mmol), palladium acetate (0.062 g, 0.3 mmol), Xantphos (0.132 g, 0.3 mmol), cesium carbonate (0.9 g, 2.8 mmol) and 4-methoxybenzylamine (0.4 ml, 2.8 mmol) in 10 ml of dimethylformamide were stirred in a sealed tube and irradiated for 10 min at 100 W in a microwave. After cooling, the reaction mixture was poured into water (100 mL), and then extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by column chromatography over silica gel with acetone/cyclohexane (5/5). The resulting oil was taken up into 20 mL of diethyl ether and a HCl gas-saturated solution of diethyl ether was cautiously added to produce a precipitate, which was collected by filtration and recrystallized from acetonitrile to give **2** as a yellow solid; Yield 40%, mp 194–196 °C. IR (KBr), cm^{-1}: 3304 (NH), 3000–2416 ($NH_2^+Cl^-$), 1650 (C=O). ^1H NMR (DMSO-d_6): δ_H 1.80 (s, 3H, CH_3), 3.05 (t, 2H, J = 6.6 Hz, CH_2), 3.30 (m, 2H, CH_2-a), 3.70 (s, 3H, OCH_3), 4.45 (s, 2H, CH_2-b), 6.87 (d, 2H, J = 8.6 Hz, H-2′), 7.15–7.28 (m, 3H, H-3, 6 and 8), 7.38–7.44 (m, 3H, H-2 and 3′), 7.61 (d, 1H, J = 7.7 Hz, H-4), 7.75 (d, 1H, J = 8.8 Hz, H-5), 8.02 (br s, 1H, NH), 8.33 (br s, 2H, NH_2). MS: m/z = 349 $[M + H]^+$.

5.4. *N-[2-(7-amino-naphth-1-yl)ethyl]acetamide (**3**)*

To a solution of the free amino compound of **2** (3 g, 8.5 mmol) in 50 ml of methanol was added 0.3 g of 10% activated charcoal-palladium. The mixture was placed under hydrogen atmosphere (atmospheric pressure) and stirred for 12 h at room temperature. The catalyst was then filtrated and the filtrate was evaporated to dryness under reduced pressure to give **3** as brown oil, yield 62%, which was engaged without further purification in the next step. IR (KBr), cm^{-1}: 3408 and 3340 (NH, NH_2), 1651 (C=O). ^1H NMR (DMSO-d_6): δ_H 1.95 (s, 3H, CH_3), 3.15 (t, 2H, J = 7.0 Hz, CH_2-a), 3.55–3.65 (m, 4H, CH_2-b and NH_2), 5.60 (br s, 1H, NH), 6.95 (dd, 1H, J = 8.6, 2.2 Hz, H-6), 7.17–7.25 (m, 3H, H-2, 3 and 8), 7.61 (d, 1H, J = 7.9 Hz, H-4), 7.68 (d, 1H, J = 8.6 Hz, H-5). MS: m/z = 229 $[M + H]^+$.

5.5. *N-[2-(7-methoxycarbonylamino-naphth-1-yl)ethyl] acetamide (**4**)*

To a vigourously stirred mixture of **3** (1 g, 4.38 mmol) in ethyl acetate (70 mL) and water (30 mL) were added potassium carbonate (908 mg, 6.57 mmol) and methyl chloroformate (0.41 mL, 5.26 mmol). After 1 h, the organic layer was washed with water, dried over $MgSO_4$ and concentrated. The residue was recrystallized from toluene to give **4** as a white solid; Yield 67%, mp 163–164 °C. IR (KBr), cm^{-1}: 3410, 3240 (NH), 1706 (C=O amid), 1650 (C=O carbamate). ^1H NMR (DMSO-d_6): δ_H 1.94 (s, 3H, CH_3), 3.14 (t, 2H, J = 7.2 Hz, CH_2), 3.38 (m, 2H, CH_2), 3.62 (s, 3H, CO_2CH_3), 6.92 (dd, 1H, J = 8.5, 2.3 Hz, H-6), 7.20–7.30 (m, 3H, H-2, 3 and 8), 7.62 (d, 1H, J = 7.9 Hz, H-4), 7.71 (d, 1H, J = 8.5 Hz, H-5), 7.96 (br s, 1H, NH), 8.70 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ_C 23.03 (CH_3), 32.78 (C-b), 40.07 (C-a), 52.28 (C-OCH_3), 111.06 (C-8), 118.98 (C-6), 124.20 (C-3), 126.88 (C-4), 127.14 (C-2), 129.65 (C-5), 130.48 (C-10), 132.33 (C-9), 134.25 (C-1), 135.96 (C-7), 154.96 (C=O), 170.55 (C-1′). MS: m/z = 287 $[M + H]^+$. Anal. Calc. for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78; Found: C, 67.24; H, 6.38; N, 9.58.

5.6. *4-(Methylsulfanyl-phenyl)-4-oxo-butyric acid (**5**) [24]*

To a cooled solution at 0 °C of thioanisole (20 mL, 170 mmol) in 1,1,2,2-tetrachloroethane (140 mL) were successively added succinic anhydride (17 g, 170 mmol) and portionwise anhydrous aluminum chloride (45.5 g, 340 mmol). The reaction mixture was then stirred and heated at 60 °C for 3 h. After cooling, it was poured into ice-cold water (500 mL) within 50 mL of concentrated HCl. The resulting precipitate was filtered, washed with water, dried, and recrystallized from ethyl acetate to give **5** as a white solid; Yield 67%, mp 153–154 °C (litt. [24] 153 °C). IR (KBr), cm^{-1}: 3300–2400 (OH), 1700 (C=O acid), 1670 (C=O cetone). ^1H NMR (DMSO-d_6): δ_H 2.54 (t, 2H, J = 6.2 Hz, CH_2-a), 2.59 (s, 3H, SCH_3), 3.21 (t, 2H,

$J = 6.2$ Hz, CH_2-b), 7.36 (d, 2H, $J = 8.3$ Hz, H), 7.90 (d, 2H, $J = 8.3$ Hz, H), 12.15 (s, 1H, CO_2H). Anal. Calc. for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39; O, 21.40; Found: C, 59.01; H, 5.36; O, 21.36.

5.7. 4-(4-Methylsulfanyl-phenyl)butyric acid (**6**)

To a cooled solution of **5** (19.8 g, 88 mmol) at 0 °C in trifluoroacetic acid (68 mL, 881 mmol) was added dropwise triethylsilane (35.2 mL, 220 mmol). After 17 h, the mixture was poured onto ice. The resulting precipitate was filtered, washed with water then with cyclohexane, and dried. Purification was accomplished by column chromatography over silica gel with acetone/toluene/cyclohexane (3:5:2) to give **6** as white crystals; Yield 94%, mp 53–55 °C (litt. [24] 49–50 °C). IR (KBr), cm^{-1}: 33040–2200 (OH), 1750 (C=O). ^1H NMR (DMSO-d_6): δ_H 1.94 (q, 2H, $J = 7.4$ Hz, CH_2-a), 2.37 (t, 2H, $J = 7.4$ Hz, CH_2-b), 2.47 (s, 3H, SCH_3), 2.64 (t, 2H, $J = 7.7$ Hz, CH_2-c), 7.11 (d, 2H, $J = 8.0$ Hz, H-2 and 6), 7.20 (d, 2H, $J = 8.0$ Hz, H-3 and 5). Anal. Calc. for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71; S, 15.25; Found: C, 62.92; H, 6.65; S, 15.15.

5.8. 7-Methylsulfanyl-3,4-dihydro-2H-naphthalen-1-one (**7**) [25]

A mixture of **6** (10 g, 52 mmol) and PPA (100 g) was mechanically stirred at 70 °C for 2 h. After cooling this reaction mixture was poured onto ice, and then extracted with diethyl ether (3 × 150 mL). The organic layer was washed with water, 1 N K_2CO_3 solution, and water again. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by column chromatography over silica gel with dichloromethane to yield **7** as yellow oil; Yield 66%. IR (KBr), cm^{-1}: 1670 (C=O). ^1H NMR (DMSO-d_6): δ_H 2.14 (q, 2H, $J = 6.3$ Hz, CH_2-a), 2.52 (s, 3H, SCH_3), 2.64 (t, 2H, $J = 6.5$ Hz, CH_2-b), 2.93 (t, 2H, $J = 6.0$ Hz, CH_2-c), 7.18 (d, 1H, $J = 8.1$ Hz, H-5), 7.38 (dd, 1H, $J = 2.1$, 8.1 Hz, H-6), 7.90 (d, 1H, $J = 2.1$ Hz, H-8). Anal. Calc. for $C_{11}H_{12}OS$: C, 68.71; H, 6.29; O, 8.32; Found: C, 68.76; H, 6.25; O, 8.35.

5.9. (7-Methylsulfanyl-3,4-dihydro-2H-naphth-1-ylidene) acetonitrile (**8**)

To a pre-cooled suspension at 0 °C of sodium hydride (2.24 g, 46.8 mmol) in anhydrous THF (50 mL) was added dropwise, under nitrogen atmosphere, a solution of diethyl cyanomethyl phosphonate (7.6 mL, 46.8 mmol) in anhydrous THF (20 mL). The mixture was kept at 0 °C for another 30 min before adding **7** (6 g, 31.2 mmol) dissolved in anhydrous THF (30 mL). After stirring at room temperature for 3 h, this reaction mixture was hydrolyzed, and then extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by column chromatography over silica gel with dichloromethane/petroleum ether (5:5) to give **8** as a yellow oil, yield 89%, which was composed by the two isomers *E*/*Z* in proportions 4:1 [the isomer *E* could be isolated as a white solid by trituration in a mixture toluene/hexane (1:5)]; mp 60–61 °C. IR (KBr), cm^{-1}: 2200 (C≡N). ^1H NMR (DMSO-d_6): δ_H 1.92 (q, 2H, $J = 6.3$ Hz, CH_2-2), 2.49 and 2.54 (2 s, 3H, SCH_3 isomers *E* and *Z* respectively), 2.81–2.89 (m, 4H, CH_2-1 and 3), 5.28 and 5.72 (2 s, 1H, CH isomers *Z* and *E* respectively), 7.11 (d, 1H, $J = 8.0$ Hz, H-5), 7.24 (dd, 1H, $J = 1.8$, 8.0 Hz, H-6), 7.43 (d, 1H, $J = 1.8$ Hz, H-8). Anal. Calc. for $C_{13}H_{13}NS$: C, 72.52; H, 6.09; N, 6.51; Found: C, 72.60; H, 6.12; N, 6.61.

5.10. (7-Methylsulfanyl-naphth-1-yl)acetonitrile (**9**)

A mixture of **8** (2 g, 9.30 mmol) and sulfur (360 mg, 11 mmol) was carried in fusion (>230 °C) for 10 h. After cooling the residue was hydrolyzed, and then extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by column chromatography over silica gel with ethyl acetate/cyclohexane (1:4) to give **9** as a beige solid; Yield 64%, mp 71–72 °C. IR (KBr), cm^{-1}: 2240 (C≡N). ^1H NMR (DMSO-d_6): δ_H 2.62 (s, 3H, SCH_3), 4.49 (s, 2H, CH_2-a), 7.44 (t, 1H, $J = 7.6$ Hz, H-3), 7.50 (dd, 1H, $J = 1.5$, 8.8 Hz, H-6), 7.58 (d, 1H, $J = 7.2$ Hz, H-2), 7.71 (s, 1H, H-8), 7.91 (m, 2H, H-4 and 5). Anal. Calc. for $C_{13}H_{11}NS$: C, 73.20; H, 5.20; N, 6.57; Found: C, 73.31; H, 5.26; N, 6.61.

5.11. 2-(7-Methylsulfanyl-naphth-1-yl)ethylamine hydrochloride (**10**)

To a solution of 1 M BH_3-THF (27 mL, 27 mmol) was added, under nitrogen atmosphere, a solution of compound **9** (1.90 g, 9.0 mmol) in anhydrous THF (30 mL). The reaction mixture was refluxed for 5 h. Then a 1 M HCl solution (18 mL, 108 mmol) was added cautiously by maintening the reflux for another 30 min. After cooling the mixture was extracted with ethyl acetate (3 × 100 mL). The aqueous layer was basified with a 4 M NaOH solution and extracted again with ethyl acetate (3 × 100 mL). The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated. Purification of the amine of **10** was accomplished by column chromatography over silica gel with dichloromethane/methanol (5:5) then methanol/ammonia (95:5). The residue was taken up with a solution of HCl gas-saturated diethyl ether, the resulting precipitate was then filtered and dried to yield **10** as a white solid; Yield 75%, mp 198–199 °C. IR (KBr), cm^{-1}: 3200–2600 (NH_3^+). ^1H NMR (DMSO-d_6): δ_H 2.65 (s, 3H, SCH_3), 3.05 (t, 2H, $J = 7.8$ Hz, CH_2-a), 3.36 (m, 2H, CH_2-b), 7.31–7.92 (m, 6H, H-2, 3, 4, 5, 6 and 8), 8.29 (br s, 3H, NH_3^+). Anal. Calc. for $C_{13}H_{16}ClNS$: C, 61.52; H, 6.35; N, 5.52; Found: C, 61.60; H, 6.33; N, 5.45.

5.12. N-[2-(7-methylsulfanyl-naphth-1-yl)ethyl]acetamide (**11**)

To a cold solution of **10** (400 mg, 1.84 mmol) in 3 mL of dichloromethane/water (2:1) were added successively potassium carbonate (511 mg, 3.68 mmol) and acetyl chloride (144 μL, 2.03 mmol). After stirring vigorously for 30 min at room temperature, the two layers were separated. The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated. The oily residue was purified by column chromatography over silica gel with acetone/toluene/cyclohexane (3/5/2) to give **11** as a white solid; Recrystallized from toluene/cyclohexane, yield 57%, mp 104–106 °C. IR (KBr), cm^{-1}: 3270 (NH), 1620 (C=O). ^1H NMR (DMSO-d_6): δ_H 1.95 (s, 3H, CH_3), 2.64 (s, 3H, SCH_3), 3.27 (t, 2H, $J = 7.2$ Hz, CH_2-a), 3.61 (m, 2H, CH_2-b), 5.54 (s, 1H, NH), 7.25–7.38 (m, 2H, H-2 and 3), 7.40 (dd, 1H, $J = 1.8$, 8.6 Hz, H-6), 7.69 (d, 1H, $J = 7.5$ Hz, H-4), 7.76 (d, 1H, $J = 8.6$ Hz, H-5), 7.88 (d, 1H, $J = 1.8$ Hz, H-8). ^{13}C NMR ($CDCl_3$): δ_C 15.82 (CH_3), 23.23 (SCH_3), 32.76 (C-b), 40.26 (C-a), 119.37 (C-8), 124.77 (C-6), 125.37 (C-3), 127.07 (C-4), 127.29 (C-2), 129.00 (C-5), 131.62 (C-10), 132.40 (C-9), 133.85 (C-1), 136.70 (C-7), 170.26 (C=O). Anal. Calc. for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40; Found: C, 61.78; H, 6.44; N, 5.36.

5.13. General procedure for oxidation of N-[2-(7-methylsulfanyl-naphth-1-yl)ethyl]acetamide **11** (**12** and **13**)

To a cold solution of **11** (0.4 g, 1.54 mmol) in anhydrous dichloromethane (20 mL) was added dropwise a solution of *m*-chloroperoxybenzoic acid (1 or 3 equivalents according to obtain respectively either **12** or **13**) in anhydrous dichloromethane (10 mL). After 2 h, the reaction mixture was evaporated to dryness under reduced pressure. The residue was taken up into saturated

Na_2CO_3 solution and the resulting precipitate was filtered, washed with water, dried and, recrystallized from toluene.

*5.13.1. N-[2-(7-methylsulfinyl-naphth-1-yl)ethyl]acetamide (**12**)*

Yield 88%, white solid, mp 101–102 °C. IR (KBr), cm^{-1}: 3420 (NH), 1651 (C=O), 1035 (S=O sulfinyl). ^1H NMR (DMSO-d_6): δ_H 1.98 (s, 3H, CH_3), 2.83 (s, 3H, $SOCH_3$), 3.35 (t, 2H, J = 7.3 Hz, CH_2-a), 3.61 (m, 2H, J = 7.0 Hz, CH_2-b), 5.82 (br s, 1H, NH), 7.45 (d, 1H, J = 7.1 Hz, H-2), 7.53 (t, 1H, J = 7.6 Hz, H-3), 7.65 (dd, 1H, J = 1.5, 8.7 Hz, H-6), 7.82 (d, 1H, J = 8.0 Hz, H-4), 8.02 (d, 1H, J = 8.7 Hz, H-5), 8.46 (s, 1H, H-8). ^{13}C NMR ($CDCl_3$): δ_C 23.32 (CH_3), 32.65 (SCH_3), 40.27 (C-b), 43.97 (C-a), 120.89 (C-a), 124.77 (C-8), 127.00 (C-6), 127.89 (C-3), 128.21 (C-4), 128.91 (C-2), 130.19 (C-5), 130.97 (C-10), 135.85 (C-9), 137.10 (C-1), 137.75 (C-7), 169.87 (C=O). Anal. Calc. for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09; S, 11.64; Found: C, 65.19; H, 6.04; N, 5.19; S, 11.46.

*5.13.2. N-[2-(7-methylsulfonyl-naphth-1-yl)ethyl]acetamide (**13**)*

Yield 63%, white solid, mp 137–142 °C. IR (KBr), cm^{-1}: 3400 (NH), 1671 (C=O), 1297 and 1143 (S=O sulfonyl). ^1H NMR (DMSO-d_6): δ_H 1.99 (s, 3H, CH_3), 3.18 (s, 3H, SO_2CH_3), 3.37 (t, 2H, J = 7.3 Hz, CH_2-a), 3.63 (m, 2H, J = 5.1 Hz, CH_2-b), 5.64 (br s, 1H, NH), 7.50 (d, 1H, J = 7.3 Hz, H-2), 7.62 (t, 1H, J = 7.7 Hz, H-3), 7.85 (d, 1H, J = 8.2 Hz, H-4), 7.94 (dd, 1H, J = 1.7, 8.6 Hz, H-6), 8.05 (d, 1H, J = 8.6 Hz, H-5), 8.77 (s, 1H, H-8). ^{13}C NMR ($CDCl_3$): δ_C 23.18 (CH_3), 32.61 (SCH_3), 40.33 (C-b), 44.39 (C-a), 121.90 (C-8), 124.72 (C-6), 127.20 (C-3), 128.35 (C-4), 128.95 (C-2), 130.59 (C-5), 130.91 (C-10), 135.85 (C-9), 137.02 (C-1), 137.67 (C-7), 170.42 (C=O). Anal. Calc. for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81; S, 11.00; Found: C, 61.70; H, 5.96; N, 5.79; S, 11.17.

*5.13.3. N-[2-(7-benzylsulfanyl-naphth-1-yl)ethyl]acetamide (**14**)*

To a stirred solution of *N*-[2-(7-hydroxy-naphth-1-yl)ethyl] acetamide (1 g, 4.4 mmol) in trifluoromethanesulfonic acid (1.17 mL, 13.2 mmol) was slowly added benzyl mercaptan (0.78 mL, 6.6 mmol) under nitrogen atmosphere. The reaction mixture was heated at 65 °C for 2–3 h. After cooling the mixture was poured into ice-cold water (50 mL) and then extracted with ethyl acetate. The organic layer was washed successively with water, 2% aqueous NaOH and water, and then dried over $MgSO_4$. The solvent was removed and the oily residue was purified by column chromatography over silica gel with dichloromethane/ethyl acetate (1:1) to give **14** as a white solid; Recrystallized from toluene/cyclohexane, yield 48%, mp 80–83 °C, IR (KBr), cm^{-1}: 3292 (NH), 1638 (C=O). ^1H NMR ($CDCl_3$): δ_H 1.92 (s, 3H, CH_3), 3.13 (t, 2H, J = 6.8 Hz, CH_2-a), 3.46 (m, 2H, CH_2-b), 4.25 (s, 2H, SCH_2), 5.38 (s, 1H, NH), 7.21–7.43 (m, 8H, H-2,3,4,2′,3′,4′,5′ and 6′), 7.67 (d, 1H, J = 8.6 Hz, H-6), 7.73 (d, 1H, J = 8.6 Hz, H-5), 8.02 (d, 1H, J = 1.8 Hz, H-8). Anal. Calc. for $C_{21}H_{21}NOS$: C, 75.19; H, 6.31; N, 4.18; Found: C, 75.23; H, 6.41; N, 4.10.

*5.13.4. [8-(2-acetylamino-ethyl)naphth-2-yl]sulfonyl chloride (**15**)*

A mixture of HCl–silica gel [28] (107 g), iodosylbenzene (2.88 g, 13.1 mmol) (freshly prepared from diacetoxyiodobenzene by the method described by Saltzmann [29]), and **14** (1 g, 3 mmol), all solid, were placed into a mortar. The mixture was well crushed and ground with a pestle at room temperature for 10 min. The solid mixture was washed with dichloromethane (3 × 200 mL), then acetone (3 × 200 mL). The combined organic layers were evaporated *in vacuo*. The residue was triturated with petroleum ether to give **15** as a pale yellow solid, yield 54%, which was kept *in vacuo* under P_2O_5 because it was hygroscopic. IR (KBr), cm^{-1}: 3420 (NH), 1652 (C=O), 1370 and 1174 (SO_2). ^1H NMR ($CDCl_3$): δ_H 1.98 (s, 3H, CH_3), 3.38 (t, 2H, J = 7.1 Hz, CH_2-a), 3.64 (m, 2H, CH_2-b), 5.67 (s, 1H, NH), 7.55 (d, 1H, J = 7.1 Hz, H-2), 7.68 (m, 1H, H-3), 7.86 (d, 1H, J = 7.8 Hz, H-4), 8.01 (dd, 1H, J = 1.9, 8.4 Hz, H-6), 8.08 (d, 1H, J = 9.0 Hz, H-5), 8.82 (s, 1H, H-8). Anal. Calc. for $C_{14}H_{14}ClNO_3S$: C, 53.93; H, 4.53; N, 4.49; Found: C, 53.86; H, 4.65; N, 4.42.

*5.14. General procedure for the preparation of N-[2-(7-alkylsulfamoyl-naphth-1-yl)ethyl]acetamides (**16** and **17**)*

To a stirred solution of **15** (0.25 g, 0.8 mmol) in dichloromethane (10 mL) was added triethylamine (0.17 mL, 1.2 mmol). The reaction mixture was cooled with ice bath, and then the appropriate amine (1.2 mmol) was slowly added. After stirring for 2 h the solvent was evaporated to dryness under reduced pressure and the resulting residue was recrystallized from suitable solvents.

*5.14.1. N-[2-(7-sulfamoyl-naphth-1-yl)ethyl]acetamide (**16**)*

Recrystallized from ethyl acetate, yield 87%, white solid. mp 194–196 °C. IR (KBr), cm^{-1}: 3371 (NH sulfonamide), 3295 (NH amide), 1654 (C=O), 1321 and 1162 (SO_2NH). ^1H NMR (DMSO-d_6): δ_H 1.80 (s, 3H, CH_3), 3.22 (t, 2H, J = 7.0 Hz, CH_2-a), 3.41 (m, 2H, CH_2-b), 7.48 (s, 2H, NH_2), 7.50 (d, 1H, J = 7.4 Hz, H-2), 7.61 (m, 1H, H-3), 7.88–7.93 (m, 2H, H-4 and 6), 8.06 (t, 1H, J = 5.2 Hz, NH), 8.13 (d, 1H, J = 8.7 Hz, H-5), 8.58 (s, 1H, H-8). ^{13}C NMR (DMSO-d_6): δ_C 22.61 (CH_3), 31.97 (C-b), 45.51 (C-a), 121.73 (C-8), 126.72 (C-6), 127.85 (C-3), 128.01 (C-4), 129.84 (C-2), 130.40 (C-5), 130.97 (C-10), 134.43 (C-9), 137.00 (C-1), 141.32 (C-7), 169.49 (C=O). Anal. Calc. for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58; Found: C, 57.31; H, 5.49; N, 9.22.

*5.14.2. N-[2-(7-methylsulfamoyl-naphth-1-yl)ethyl]acetamide (**17**)*

Recrystallized from toluene, yield 95%, white solid, mp 155–156 °C. IR (KBr), cm^{-1}: 3399 (NH sulfonamide), 3288 (NH amide), 1671 (C=O), 1315 and 1159 (SO_2NH). ^1H NMR (DMSO-d_6): δ_H 1.79 (s, 3H, CH_3), 2.44 (d, 3H, J = 5.0 Hz, $NHCH_3$), 3.23 (t, 2H, J = 7.1 Hz, CH_2-a), 3.40 (m, 2H, CH_2-b), 7.52 (d, 1H, J = 7.1, H-2), 7.56 (q, 1H, J = 5.0 Hz, NH), 7.64 (m, 1H, H-3), 7.82 (dd, 1H, J = 1.0, 8.6 Hz, H-6), 7.94 (d, 1H, J = 8.0 Hz, H-4), 8.06 (br s, 1H, NH), 8.16 (d, 1H, J = 8.8 Hz, H-5), 8.53 (s, 1H, H-8). ^{13}C NMR ($CDCl_3$): δ_C 23.09 (CH_3), 29.51 (NCH_3), 33.15 (C-b), 40.62 (C-a), 122.54 (C-8), 124.17 (C-6), 127.11 (C-3), 128.09 (C-4), 128.37 (C-2), 130.00 (C-5), 131.07 (C-10), 135.33 (C-9), 135.97 (C-1), 136.82 (C-7), 170.95 (C=O). Anal. Calc. for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14; Found: C, 58.46; H, 5.88; N, 8.98.

*5.15. 2-(7-Methylsulfamoyl-naphth-1-yl)ethylamine hydrochloride (**18**)*

A solution of **16** (0.43 g, 1.4 mmol) in 6 M HCl (5.8 mL, 35.1 mmol) was refluxed for 16 h and evaporated *in vacuo*. The residue was taken up with diisopropyl ether and the resulting precipitate was filtered, dried, and recrystallized from absolute ethanol to yield **18** as a white solid; Yield 71%, mp 236–238 °C. IR (KBr), cm^{-1}: 3300 (NH sulfonamide), 2946–2360 (NH_3^+), 1320 and 1137 (SO_2NH). ^1H NMR (DMSO-d_6): δ_H 2.47 (d, 3H, J = 4.9 Hz, SO_2NHCH_3), 3.17 (m, 2H, CH_2-a), 3.45 (m, 2H, CH_2-b), 7.62 (d, 1H, J = 7.3 Hz, H-2), 7.69 (m, 1H, H-3), 7.81–7.89 (m, 2H, H-6 and NH), 8.01 (d, 1H, J = 8.3 Hz, H-4), 8.20–8.27 (m, 4H, H-5$^+$ and NH_3), 8.64 (s, 1H, H-8). Anal. Calc. for $C_{13}H_{17}ClN_2O_2S$: C, 51.91; H, 5.70; N, 9.31; Found: C, 51.63; H, 5.81; N, 9.11.

*5.16. N-[2-(7-methylsulfamoyl-naphth-1-yl)ethyl]furan-2-ylcarboxamide (**19**)*

To a pre-cooled solution at 0 °C of **18** (0.5 g, 1.7 mmol) in dichloromethane (15 mL) were added successively triethylamine (0.46 mL, 3.4 mmol) and 2-furoyl chloride (0.18 mL, 1.9 mmol). After 3 h, the reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography over silica gel with dichloromethane then ethyl acetate and the resulting solid was

recrystallized from toluene to give **19** as a white solid; Yield 63%, mp 117–119 °C. IR (KBr), cm^{-1}: 3363 (NH sulfonamide), 3285 (NH amide), 1664 (C=O), 1319 and 1162 (SO_2NH). ^1H NMR ($CDCl_3$): δ_H 2.70 (d, 3H, $J = 5.5$, $NHCH_3$), 3.43 (m, 2H, CH_2-a), 3.77 (m, 2H, CH_2-b), 5.38 (m, 1H, NH), 6.52 (dd, 1H, $J = 1.8$, 3.6 Hz, H-4′), 6.72 (br s, 1H, NH), 7.15 (d, 1H, $J = 3.6$ Hz, H-3′), 7.44 (s, 1H, H-5′), 7.50 (d, 1H, $J = 6.9$ Hz, H-2), 7.58 (m, 1H, H-3), 7.84 (d, 1H, $J = 8.0$ Hz, H-4), 7.93 (dd, 1H, $J = 1.6$, 8.6 Hz, H-6), 8.02 (d, 1H, $J = 8.4$ Hz, H-5), 8.93 (s, 1H, H-8). ^{13}C NMR ($CDCl_3$): δ_C 29.55 (NCH_3), 33.28 (C-b), 40.03 (C-a), 112.06 (C-3′), 114.34 (C-2′), 122.55 (C-8), 124.08 (C-6), 127.18 (C-3), 128.08 (C-4), 128.31 (C-2), 130.05 (C-5), 130.96 (C-10), 135.33 (C-9), 136.11 (C-1), 136.35 (C-7), 144.02 (C-4′), 147.65 (C-1′), 158.72 (C=O). Anal. Calc. for $C_{18}H_{18}N_2O_4S$: C, 60.32; H, 5.06; N, 7.82; Found: C, 60.24; H, 5.00; N, 7.74.

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