ELSEVIER

Eur. J. Med. Chem. 37 (2002) 147–161

EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY

Original article

COX-1/COX-2 inhibitors based on the methanone moiety

Gerd Dannhardt [a,*], Bernd L. Fiebich [b], Johannes Schweppenhäuser [a]

[a] *Institute of Pharmacy, Fachbereich Chemie und Pharmazie, Johannes Gutenberg, University of Mainz, Staudingerweg 5, D-55099 Mainz, Germany*

[b] *Department of Psychiatry and Psychotherapy, Albert-Ludwigs-University, D-79104 Freiburg, Germany*

Received 17 July 2001; received in revised form 5 December 2001; accepted 6 December 2001

Abstract

This paper focuses on the synthesis and the in vitro testing of dual COX-1/COX-2 inhibitors. Starting from structures of non-steroidal anti-inflammatory drugs (NSAIDs) the diaryl methanone element was chosen as a lead. Modifications were carried out on this scaffold to obtain potent inhibitors of the COX enzymes. The *N*-(2-aroylphenyl)sulphonamides and -amides were studied in detail, and to consolidate the data evaluated the corresponding 3- and 4-regioisomers were also investigated. The potency and the enzyme selectivity were varied by structural modifications of the lead. © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

Keywords: *N*-(Aroylphenyl)amides and -sulphonamides; COX-1/COX-2 inhibition; Structure–activity relationships

1. Introduction

Prostaglandins are important biological mediators of inflammation, originating from biotransformation of arachidonic acid catalysed by cyclooxygenase [1]. In spite of some adverse side effects [2,3], cyclooxygenase inhibitors are the drugs to suppress inflammatory processes. Two isoenzymes of cyclooxygenase have been identified: COX-1 and COX-2 [4,5]. Selective inhibition of COX-2 [6] or dual inhibition of COX-1 and COX-2 [7] is under discussion as a promising principle in the treatment of inflammatory diseases. For several reasons, including increased cardiovascular risks, the important role of COX-2 produced prostaglandins in the response of the mucosa to irritants and in healing and other critical aspects the accuracy of selective COX-2 inhibition as the principle tenet is under debate [8–10].

A number of substituted sulphonamides are known as anti-inflammatory agents (Fig. 1) [11–13]. The first substances were diflumidone and nimesulide, which was a lead for NS-398 and flosulide. Diarylmethanones such as ketoprofen, tiaprofenic acid, tolmetine, and ketorolac are used in the therapy of inflammation.

The objective of this study was to correlate the structural parameters with the inhibitory potency and the enzyme selectivity, i.e. to evaluate the significance of

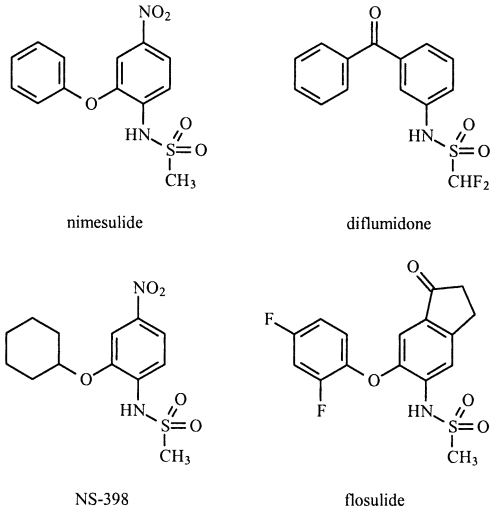


Fig. 1. Structures of COX-inhibitors.

* Correspondence and reprints.
E-mail address: dannhrdt@mail.uni-mainz.de (G. Dannhardt).

0223-5234/02/$ - see front matter © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.
PII: S0223-5234(01)01330-7

the aryl substituents, of the carbonyl-moiety as the linking element, the impact of the sulphonamide and the amide group, and the contribution of the functional moiety at different positions on the phenyl ring. In this context, we also studied the meaning of the rotation phenomena of the two aromatic rings (Fig. 2).

The compounds were tested in vitro to evaluate their COX-1/COX-2 inhibitory activity.

2. Chemistry

The compounds, synthesised are summarised in Table 1 and Fig. 3.

The synthesis of the *N*-(aroylphenyl)sulphonamides and -amides **1a**, **2a**–**h**, **5**, **6a**–**b**, **7**, **2a**–**b**, **9**, **10a**–**c**, **12a**–**c**, **13a**–**c** started with commercially available amines and sulphonyl chlorides or carbonyl chlorides.

Adapted to procedures described by Walsh [14] and Miyachi et al. [15], 2-aminobenzoic acid with methanesulphonyl chloride in aqueous sodium carbonate gave rise to 2-methylsulphonylamido benzoic acid which was transformed to the chloride and subsequently by Friedel-Crafts acylation to *N*-(aroylphenyl)sulphonamides **1b**–**c** (Fig. 4).

The synthesis of **1d** is likewise possible but to obtain a compound with greater purity we chose the procedure of Guilhemat et al. [16] and reacted 1-phenylbenzene isatoic anhydride and $AlCl_3$ at 110 °C for 8 h. The corresponding amine together with methanesulphonyl chloride yielded the desired product **1d** (Fig. 5).

Another strategy was used to synthesise **1e**, **2i** and **2j**. The reaction sequence is outlined in Fig. 6.

2-Aminophenyl-2-thienyl methanone, the basic moiety of the compounds **3**, **4a**–**b** and **11a**–**c** was synthesised according to a procedure of Hunziker et al. [17]. The amides and sulphonamides were obtained using the corresponding sulphonyl and carbonyl chlorides.

Due to the structural complexity of this group, the sulphonamides **14**–**20** were prepared using two different strategies. Compound **17** can be obtained directly from **1a** with dimethylsulphate in absolute THF, **1a** and 1,2-ethanedithiol-boron trifluoride etherate gave rise to **18** [18], $LiAlH_4$ reduction of **1a** led to **19**. Starting material for the sulphonamides **14**–**16** and **20** were commercially available amines. In the case of **16** the 2-amino-6-methoxyphenyl-phenylmethanone was synthesised according to a procedure of Walsh [14]. The data of the compounds are summarised in Table 2.

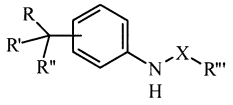
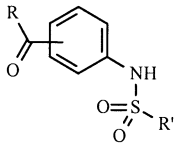
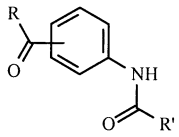


Fig. 2. R = aryl; R′R″ = O; R′ = OH, R″ = H; R′,R″ = H; R‴ = CH_3, aryl; X = SO_2, CO.

Table 1
N-(Aroylphenyl)sulphonamides and -amides



1a–8b



9–13c

Compound	R	R′	RCO-position
1a	ph	CH_3	2
1b	4-CH_3–ph	CH_3	2
1c	4-CH_3–S–ph	CH_3	2
1d	4-ph–ph	CH_3	2
1e	4-*tert*-butyl–ph	CH_3	2
2a	ph	ph	2
2b	ph	4-CH_3–ph	2
2c	ph	4-Cl–ph	2
2d	ph	4-CH_3–O–ph	2
2e	ph	4-*tert*-butyl–ph	2
2f	ph	3,5-bis-tri-F–ph	2
2g	ph	2-naphthyl	2
2h	ph	2-thienyl	2
2I	4-CH_3–ph	4-CH_3–ph	2
2j	4-*tert*-butyl–ph	4-CH_3–ph	2
3	2-thienyl	CH_3	2
4a	2-thienyl	4-CH_3–ph	2
4b	2-thienyl	4-Cl–ph	2
5	ph	CH_3	3
6a	ph	4-CH_3–ph	3
6b	ph	4-Cl–ph	3
7	ph	CH_3	4
8a	ph	4-CH_3–ph	4
8b	ph	4-Cl–ph	4
9	ph	CH_3	2
10a	ph	ph	2
10b	ph	4-CH_3–ph	2
10c	ph	4-Cl–ph	2
11a	2-thienyl	ph	2
11b	2-thienyl	4-CH_3–ph	2
11c	2-thienyl	4-Cl–ph	2
12a	ph	ph	3
12b	ph	4-CH_3–ph	3
12c	ph	4-Cl–ph	3
13a	ph	ph	4
13b	ph	4-CH_3–ph	4
13c	ph	4-Cl–ph	4

3. Pharmacology

The compounds were tested for their inhibitory potency against COX-1 in an intact cell assay described earlier [29]. Porcine blood was used as the enzyme source and the isolated platelets as the source for COX-1 activity. The cells were incubated with the compounds and stimulated with calcium ionophore A 23187. The amount of malondialdehyde (MDA) was determined by fluorometry. IC_{50} values were calculated with the program GRAFIT, Erithacus Software Ltd.,

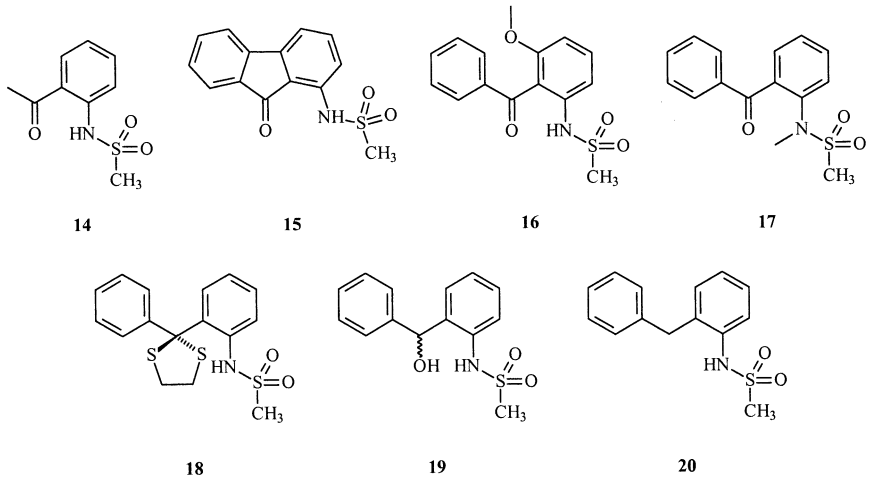


Fig. 3. Modified sulphonamides.

UK. Amfenac, diclofenac, indomethacin and ketoprofen were used as reference standards (IC_{50} values see Fig. 7).

To determine the COX-2 activity the method of Fiebich et al. [30] was applied. The inhibition of LPS-induced COX-2 in human monocytes was calculated using monocytes from the peripheral blood of healthy donors and the PGE_2 assay.

4. Results and discussion

Table 1 and Fig. 3 summarise the compounds tested. All the compounds were screened for their COX-1 inhibitory potency. Some of them were also tested to ascertain COX-2 inhibition. The results are listed in Table 3.

4.1. N-(Aroylphenyl)sulphonamides

The *N*-(2-benzoylphenyl)methanesulphonamides **1a**–**e** differ only at position 4′ of R. For none of these compounds can any noticeable inhibitory activity against COX-2 be found. The unsubstituted **1a** and the methylsulphanyl derivative **1c** inhibit COX-1 equipotently. A significant increase of inhibitory potency is observed for the 4′-methyl compound **1b** ($IC_{50} = 0.05$ μM). Bulky substituents such as a phenyl (**1d**) or a *tert*-butyl residue (**1e**) result in a lack of COX-1 inhibition. These findings are confirmed in the **2** series by **2j**.

In the arylsulphonyl series **2a**–**j** no inhibition of COX-2 are found, but most of the compounds are more potent or equipotent COX-1 inhibitors than the lead **1a**. The *para*-methylsulphonamide **2b** is the most potent COX-1 inhibitor, but the activity decreases if position 4′ of the aroyl moiety is substituted, especially with a bulky residue such as the *tert*-butyl group (**2j**).

The increase of potency of anti-inflammatories is often correlated with the lipophilicity using the thiophene approach [31] but our tests show that the thienoyl sulphonamides **3**, **4a**–**b** possess less potency than the corresponding aroyl sulphonamides **1a**–**c**. The highest inhibitory activity is found for the tosyl-sulphonamides (**1b**: 0.05; **2b**: 0.35; **4a**: 1.06 μM).

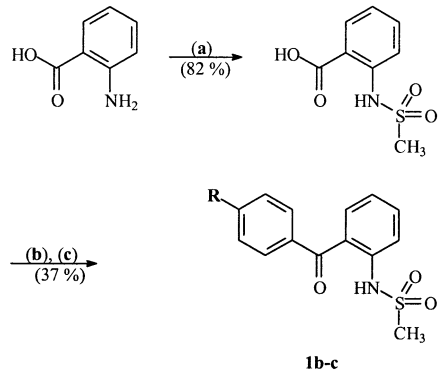


Fig. 4. (a) Cl–SO_2CH_3, aq. Na_2CO_3; (b) $SOCl_2$; (c) $AlCl_3$–C_6H_5–R, CH_2Cl_2.

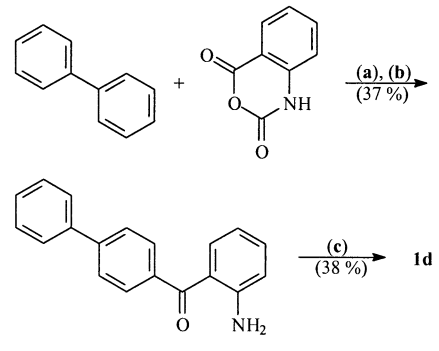


Fig. 5. (a) $AlCl_3$/110 °C/8 h; (b) concd. HCl; (c) CH_3SO_2–Cl, CH_2Cl_2–pyridine.

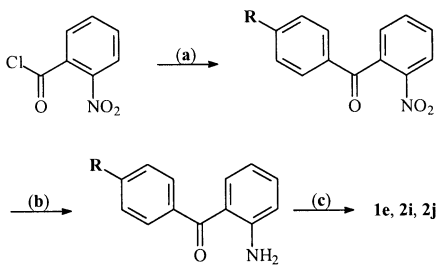


Fig. 6. (a) $AlCl_3$–C_6H_5–R, CH_2Cl_2; (b) hydrogen (10 bar), Pd–C; (c) R′–SO_2–Cl, CH_2Cl_2–pyridine.

Consequently, we investigated the regioisomeric 3- and *N*-(4-benzoylphenyl)sulphonamides **5**, **6a**, **6b** and **7**, **8a**–**b**. Compound **5** (0.25 μM) is fourfold more potent than **1a** (1.12 μM) and 16-fold more potent than **7** (4.11 μM). These results are in agreement with Harrington et al. [11] and Moore and Harrington [12] testing 3-benzoyl fluoroalkanesulphonamides. The arylsulphonamides **8a**–**b** and **6a**–**b** inhibit COX-1 in the low micromolar range. The tosylamides **8a** (0.23 μM) and **6a** (0.67 μM) are more potent than the corresponding 4-chloro-sulphonamides **8b** (0.33 μM) and **6b** (2.73 μM). In contrast to methanesulphonamides **7** the arylsulphonamide derivatives **8a** and **8b** are the most potent compounds in this series.

4.2. Modified sulphonamides

Compounds **14**–**20** show no or poor (**20**) enzyme inhibiting potency. These results indicate that modifications of the carbonyl moiety or the restriction of the rotation of both aryl rings are detrimental to the activity. Evidently the ketone function is a prerequisite for COX-1 and COX-2 potency.

4.3. N-(Aroylphenyl)benzamides

The *N*-(aroylphenyl)amides were prepared to test whether the sulphonamide moiety is pharmacophore in essence.

The benzamides **10a**–**c** inhibit the COX-1 enzyme with the activity increasing from the unsubstituted compound to the chloro derivative **10c** ($IC_{50} = 0.18$ μM).

Compounds **10a**–**c** are balanced dual inhibitors of COX-1 and COX-2 (COX-1/COX-2 ratio: 0.52–0.82).

The thienoyl-derivatives **11a**–**c** represent potent COX-1 inhibitors. Compound **11c** was identified as one of the most potent COX-1 inhibitors ($IC_{50} = 0.05$ μM), however, in contrast to the corresponding benzoyl compounds **10a**–**c** the thienoyl-derivatives **11a**–**c** inhibit the COX-2 enzyme less potently (see Table 3).

The 3-benzoyl derivatives **12a**–**c** are equipotent COX-1 inhibitors and more potent than the corresponding 4-regioisomers **13a**–**c**. Compounds **12a**–**c** and **13a**–**c** preferentially inhibit the COX-1 isoform.

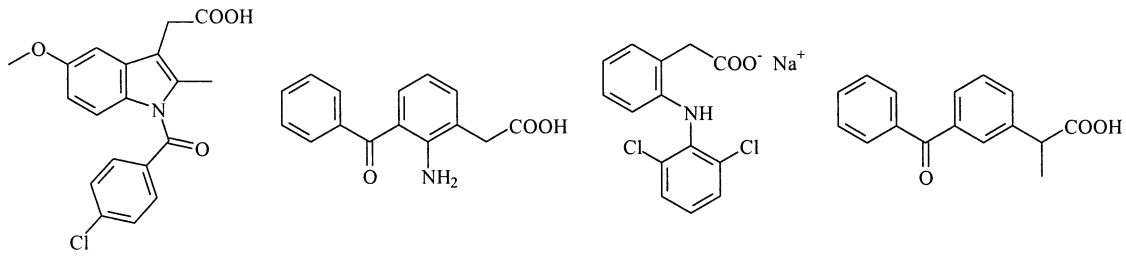
4.4. Comparison of N-(aroylphenyl)sulphonamides and N-(aroylphenyl)benzamides

As mentioned above, *N*-(aroylphenyl)sulphonamides are selective COX-1 inhibitors. Most of the investigated *N*-(aroylphenyl)benzamides are potent COX-1 and COX-2 inhibitors with a varying selectivity profile. The

Table 2
IC_{50} values of compounds tested (μM or percentage of inhibition at a concentration of 10 μM)

Compound	COX-1	COX-2	COX-1/COX-2
1a	1.12	13.7	
1b	0.05	36.9	
1c	1.31	n.t.	
1d	>10	10.3	
1e	>10	0%	
2a	0.40	n.t.	
2b	0.35	n.t.	
2c	0.58	9%	
2d	1.00	n.t.	
2e	1.70	n.t.	
2f	1.83	n.t.	
2g	1.40	n.t.	
2h	1.08	n.t.	
2i	2.95	n.t.	
2j	>10	10%	
3	2.77	n.t.	
4a	1.06	n.t.	
4b	~10	0%	
5	0.25	n.t.	
6a	0.67	n.t.	
6b	2.73	5%	
7	4.11	n.t.	
8a	0.23	n.t.	
8b	0.33	20%	
9	>10	n.t.	n.d.
10a	2.09	2.55	0.82
10b	0.32	0.61	0.52
10c	0.18	0.24	0.75
11a	0.42	2.63	0.16
11b	0.11	3.00	0.04
11c	0.05	24%	n.d.
12a	0.49	1.80	0.27
12b	0.39	3.30	0.12
12c	0.42	1.67	0.25
13a	2.93	n.t.	n.d.
13b	3.98	10	0.40
13c	0.58	25%	n.d.
14	>10	n.t.	
15	>10	n.t.	
16	>10	n.t.	
17	>10	n.t.	
18	>10	n.t.	
19	>10	n.t.	
20	>10	n.t.	

n.t., not tested; n.d., not determined.



Indomethacin
IC_{50} values [μM]:
0.0005 (COX-1)
0.0043 (COX-2)
COX-1/COX-2 ratio: 0.12

Amfenac
IC_{50} values [μM]:
0.0044 (COX-1)
0.0062 (COX-2)
COX-1/COX-2 ratio: 0.71

Diclofenac
IC_{50} values [μM]:
0.0015 (COX-1)
0.004 (COX-2)
COX-1/COX-2 ratio: 0.38

Ketoprofen
IC_{50} values [μM]:
0.0074 (COX-1)
0.063 (COX-2)
COX-1/COX-2 ratio: 0.18

Fig. 7. IC_{50} values for COX-1 and COX-2 inhibition of indomethacin, amfenac, diclofenac and ketoprofen [32].

benzamides **10a–c** are equipotent dual inhibitors of COX-1 and COX-2.

In general benzamide derivatives are more potent than the corresponding sulphonamides except the sulphonamides **2a** and **8a** which inhibit the COX-1 enzyme more potently than the benzamides **10a** and **13b**.

5. Summary and conclusions

Starting with *N*-(2-benzoylphenyl)methanesulphonamide (**1a**) as a lead, variations of the benzoyl, aniline and sulphonamide moiety were produced. In addition the exchange of benzoyl by a 2-thienoyl residue was performed. A substituent at position 4′of the 2-benzoyl moiety led to **1b**, the most potent COX-1 inhibitor. The shift from mesyl to tosyl derivatives increased COX-1-inhibition.

Based on these results the molecules were modified systematically to postulate the following structure–activity relationships:

(a) *flexibility* of the molecule seems to be a prerequisite for interaction with the amino acids of the inner surface of the COX-channel;
(b) the *carbonyl moiety* as a link between the two aryl rings allows an orientation to each other which is optimum for intermolecular bonding. In addition it is a hydrogen acceptor;
(c) the *NH-group* may serve as the donor of intermolecular hydrogen bonds;
(d) increasing lipophilicity does not enhance the COX inhibitory potency.

The corresponding 3- and 4-regioisomers reinforced the structure–activity relationships discussed above. In general, arylsulphonamides preferentially inhibit COX-1 but the corresponding amides are more potent. Some *N*-(aroylphenyl) amides are balanced dual COX-1 and COX-2 inhibitors.

6. Experimental

6.1. Chemistry

Melting points were measured on a Büchi apparatus (Dr Tottoli) and were not corrected. IR spectra (KBr disks unless otherwise stated) were recorded on a Beckmann IR Model 4220 spectrophotometer. ^{1}H-NMR-spectra were obtained on a Bruker AC 200 (200 MHz) or Bruker AC 300 (300 MHz) and were consistent with proposed structures (solvent: $CDCl_3$ unless otherwise stated). Chemical shifts are described in parts per million. Tetramethylsilane was used as internal standard. Coupling constants (*J*) are reported in Hertz. Mass spectra (electron impact) were obtained on a Varian MAT 311 A. Thinlayer chromatography (TLC) was carried out with E. Merck silica gel 60 F_{254} plates. CC were conducted over SiO_2 in glass tubes (30×500 mm) under pressure (N_2, 0.8 bar). Analyses indicated by the element symbols were within $\pm 0.4\%$ of the theoretical values. All chemicals were of analytical grade. Yields are reported in percent from their theoretically calculated value.

6.2. General procedure for the preparation of sulphonamides and carbonamides (Method A)

To a stirred and cooled (ice bath) solution of the amine and 1.5 equiv. pyridine in dry CH_2Cl_2 a solution of the $SOCl_2$, or carbonyl chloride, was added. The solution was stirred for 3 h at room temperature (r.t.) before being hydrolysed with water. The organic layer was separated, washed three times with water, Na_2CO_3 and water and finally dried with Na_2SO_4. The solvent was evaporated under reduced pressure to yield the crude product, which was usually purified by CC.

Table 3
Physical data of compounds synthesised.

Compound	m.p. (°C)	IR (KBr)	^{1}H-NMR (200 MHz), δ (ppm), J (Hz)/MS (EI, 70 eV): m/z
1a	108 (106–107 [19])	1625 (C=O), 1325, 1150 (SO_2–N)	3.08 (s, 3H, CH_3), 7.11 (ddd, $^3J = 7.9$ Hz, $^3J = 7.6$ Hz, $^4J = 1.2$ Hz, 1H, $H_{arom.}$), 7.47–7.52 (m, 2H, $H_{arom.}$), 7.56–7.64 (m, 3H, $H_{arom.}$), 7.68–7.70 (m, 2H, $H_{arom.}$), 7.81 (dd, $^3J = 8.3$ Hz, $^4J = 0.7$ Hz, 1H, $H_{arom.}$), 10.28 (s, 1H, NH) 275.0 [23%, $M^{+\bullet}$], 196.1 [30%, $M^{+\bullet} - SO_2CH_3$], 105.1 (12%, $C_6H_5CO^+$)
1b	96	1630 (C=O), 1335, 1150 (SO_2–N)	2.43 (s, 3H, $ArCH_3$), 3.04 (s, 3H, SO_2CH_3), 7.13 (dd, $^3J = 7.8$ Hz, $^3J = 7.3$ Hz, 1H, $H_{arom.}$), 7.28 (d, $^3J = 7.8$ Hz, 2H, AA′), 7.52–7.62 (m, 4H, $H_{arom.}$), 7.78 (d, $^3J = 8.3$ Hz, 1H, $H_{arom.}$), 10.11 (s, 1H, NH) 290.2 [24%, $M^{+\bullet}$], 210.8 [100%, $M^{+\bullet} - SO_2CH_3$], 119.3 (42%, $CH_3C_6H_5CO^+$), 91.3 (27%, $C_7H_7^+$)
1c	127	1630 (C=O), 1320, 1155 (SO_2–N)	2.53 (s, 3H, S–CH_3), 3.04 (s, 3H, SO_2CH_3), 7.13 (dd, $^3J = 7.8$ Hz, $^3J = 7.3$ Hz, 1H, $H_{arom.}$), 7.28 (d, $^3J = 8.8$ Hz, 2H, AA′), 7.52–7.80 (m, 5H, $H_{arom.}$), 10.00 (s, 1H, NH) 321.2 [57%, $M^{+\bullet}$], 241.9 [24%, $M^{+\bullet} - SO_2CH_3$], 194.9 (23%), 84.2 (100%)
1d	145	1640 (C=O), 1340, 1155 (SO_2–N)	3.07 (s, 3H, CH_3), 7.16 (dd, $^3J = 7.6$ Hz, 1H, $H_{arom.}$), 7.39–7.82 (m, 12H, $H_{arom.}$), 10.21 (s, 1H, NH) 351.7 [36%, $M^{+\bullet}$], 372.7 [100%, $M^{+\bullet} - SO_2CH_3$], 181.1 (22%, $C_6H_5C_6H_4CO^+$)
1e	158	1630 (C=O), 1330, 1150 (SO_2–N)	1.37 (s, 9H, *t*Bu), 3.05 (s, 3H, CH_3), 7.15 (ddd, $^3J = 7.9$ Hz, $^3J = 7.4$ Hz, $^4J = 1.2$ Hz, 1H, $H_{arom.}$), 7.51 (d, $^3J = 8.5$ Hz, 2H, AA′), 7.58 (ddd, $^3J = 7.9$ Hz, $^3J = 7.6$ Hz, $^4J = 1.7$ Hz, 1H, $H_{arom.}$), 7.66 (d, $^3J = 8.3$ Hz, 2H, BB′), 7.66 (d, $^3J = 8.3$ Hz, 2H, BB′), 7.80 (dd, $^3J = 8.3$ Hz, $^4J = 1.0$ Hz, 1H, $H_{arom.}$), 10.16 (s, 1H, NH) 331.6 [48%, $M^{+\bullet}$], 251.1 [21%, $M^{+\bullet} - SO_2CH_3$], 237.0 (41%), 196.3 (100%), 56.0 (79%)
2a	135	1625 (C=O), 1320, 1170 (SO_2–N)	7.07 (dd, $^3J = 7.8$ Hz, $^4J = 1.0$ Hz, 1H, $H_{arom.}$), 7.23–7.59 (m, 10H, $H_{arom.}$), 7.67–7.80 (m, 3H, $H_{arom.}$), 10.14 (s, 1H, NH) 337.2 [34%, $M^{+\bullet}$], 196.3 [100%, $M^{+\bullet} - SO_2CH_3$], 105.0 (14%, $C_6H_5CO^+$), 77.0 (53%, $C_6H_5^+$)
2b	119 (127 [20])	1630 (C=O), 1390, 1165 (SO_2–N)	2.20 (s, 3H, CH_3), 7.01 (d, $^3J = 7.9$ Hz, 2H, AA′), 7.06–7.10 (m, 1H, $H_{arom.}$), 7.34–7.40 (m, 5H, $H_{arom.}$), 7.47–7.56 (m, 4H, $H_{arom.}$), 7.76–7.78 (m, 1H, $H_{arom.}$), 9.97 (s, 1H, NH) 351.4 [61%, $M^{+\bullet}$], 196.1 [100%, $M^{+\bullet} - SO_2C_6H_4CH_3$], 91.4 (37%, $C_7H_7^+$)
2c	124	1630 (C=O), 1320, 1175, (SO_2–N)	7.09–7.79 (m, 14H, $H_{arom.}$), 9.96 (s, 1H, NH) 371.7 [26%, $M^{+\bullet}$], 196.3 [100%, $M^{+\bullet} - SO_2C_6H_4Cl$], 77.2 (24%, $C_6H_5^+$)
2d	98 (92–100 [21])	3260 (N–H), 1635 (C=O), 1345, 1160 (SO_2–N)	3.67 (s, 3H, OCH_3), 6.67 (d, $^3J = 8.8$ Hz, 2H, AA′), 7.08 (dd, $^3J = 7.8$ Hz, $^3J = 7.83$ Hz, 1H, $H_{arom.}$), 7.34–7.62 (m, 9H, $H_{arom.}$), 7.77 (d, $^3J = 8.3$ Hz, 1H, $H_{arom.}$), 9.92 (s, 1H, NH) 367.5 [64%, $M^{+\bullet}$], 196.4 [100%, $M^{+\bullet} - SO_2C_6H_4OCH_3$], 171.2 (46%, $SO_2C_6H_4OCH_3^+$), 107.2 (43%, $C_6H_4OCH_3^+$), 77.3 (51%, $C_6H_5^+$)
2e	135	3180 (N–H), 1640 (C=O), 1345, 1180 (SO_2–N)	1.18 (s, 9H, *t*Bu), 7.08 (dd, $^3J = 7.8$ Hz, $^3J = 7.3$ Hz, 1H, $H_{arom.}$), 7.29 (d, $^3J = 8.5$ Hz, 2H, AA′), 7.35–7.55 (m, 7H, $H_{arom.}$), 7.62 (d, $^3J = 8.5$ Hz, 2H, BB′), 7.80 (d, $^3J = 8.3$ Hz, 1H, $H_{arom.}$), 10.17 (s, 1H, NH) 393.7 [31%, $M^{+\bullet}$], 196.3 [100%, $M^{+\bullet} - SO_2C_6H_4tBu$]
2f	98	3250 (N–H), 1645 (C=O), 1365, 1130 (SO_2–N)	7.18–7.82 (m, 10H, $H_{arom.}$), 8.06 (s, 1H, $H_{arom.}$), 10.00 (s, 1H, NH) 474.4 [22%, $M^{+\bullet}$], 196.8 (100%)
2g	118	3180 (N–H), 1640 (C=O), 1340, 1170 (SO_2–N)	7.01–7.86 (m, 15H, $H_{arom.}$), 8.20 (s, 1H, $H_{arom.}$), 10.07 (s, 1H, NH) 387.2 [68%, $M^{+\bullet}$], 196.2 [100%, $M^{+\bullet} - SO_2C_{10}H_7$], 127.5 (68%, $C_{10}H_7^+$)
2h	124	1630 (C=O), 1325, 1155 (SO_2–N)	6.84 (dd, $^3J = 3.9$ Hz, $^4J = 1.5$ Hz, 1H, $thiophen_{H\text{-}4}$), 7.12 (dd, $^3J = 7.8$ Hz, $^4J = 1.5$ Hz, 1H, $H_{arom.}$), 7.35–7.61 (m, 9H, $H_{arom.}$), 7.84 (d, $^3J = 8.3$ Hz, 1H, $H_{arom.}$), 10.22 (s, 1H, NH) 343.4 [45%, $M^{+\bullet}$], 278.5 (23%), 196.5 [100%, $M^{+\bullet} - SO_2C_4H_3S$], 147.1 (10%, $SO_2C_4H_3S^+$), 105.3 (29%, $C_6H_5CO^+$), 77.3 (36%, $C_6H_5^+$)

Table 3 (continued).

Compound	m.p. (°C)	IR (KBr)	^{1}H-NMR (200 MHz), δ (ppm), J (Hz)/MS (EI, 70 eV): m/z
2i	125 (123 [20])	1630 (C=O), 1320, 1155 (SO_2–N)	2.21 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 7.01 (d, $^3J = 7.9$ Hz, 2H, AA′), 7.09 (dd, $^3J = 7.6$ Hz, $^4J = 1.2$ Hz, 1H, $H_{arom.}$), 7.18 (d, $^3J = 7.9$ Hz, 2H, AA′), 7.29 (d, $^3J = 8.3$ Hz, 2H, BB′), 7.36 (dd, $^3J = 7.9$ Hz, $^4J = 1.4$ Hz, 1H, $H_{arom.}$), 7.50 (dd, $^3J = 8.3$ Hz, $^4J = 1.4$ Hz, 1H, $H_{arom.}$), 7.54 (d, $^3J = 8.3$ Hz, 2H, BB′), 7.78 (dd, $^3J = 8.3$ Hz, $^4J = 1.0$ Hz, 1H, $H_{arom.}$), 9.88 (s, 1H, NH) 365.2 [32%, $M^{+\bullet}$], 210.2 [100%, $M^{+\bullet} - SO_2C_6H_4CH_3$], 91.1 (42%, $C_7H_7^+$)
2j	118	3250 (N–H), 1630 (C=O), 1600, 1340, 1170 (SO_2–N)	1.35 (s, 9H, *t*Bu), 2.21 (s, 3H, CH_3), 7.01 (d, $^3J = 8.1$ Hz, 2H, AA′), 7.09 (ddd, $^3J = 7.6$ Hz, $^4J = 1.0$ Hz, 1H, $H_{arom.}$), 7.31–7.56 (m, 8H, $H_{arom.}$), 7.77–7.80 (m, 1H, $H_{arom.}$) 9.94 (s, 1H, NH) 407.0 [47%, $M^{+\bullet}$], 196.1 (100%), 91.1 (28%, $C_7H_7^+$), 57.6 (36%, tBu^+)
3	yellow liquid	3280 (N–H), 1625 (C=O), 1340, 1170 (SO_2–N)	3.01 (s, 3H, CH_3), 7.15–7.21 (m, 2H, $H_{arom.}$), 7.53–7.61 (m, 2H, $H_{arom.}$), 7.76–7.89 (m, 3H, $H_{arom.}$), 7.86 (dd, $^3J = 7.8$ Hz, $^4J = 1.5$ Hz, 1H, $H_{arom.}$), 9.55 (s, 1H, NH) 281.8 [20%, $M^{+\bullet}$], 202.4 [37%, $M^{+\bullet} - SO_2CH_3$]
4a	124 (125 [22])	3230 (N–H), 1310, 1170 (SO_2–N)	2.14 (s, 3H, CH_3), 6.91 (d, $^3J = 8.3$ Hz, 2H, AA′), 7.01–7.10 (m, 2H, $H_{arom.}$), 7.17 (ddd, $^3J = 7.8$ Hz, $^4J = 1.5$ Hz, 1H, $H_{arom.}$), 7.44 (d, $^3J = 8.3$ Hz, 2H, BB′), 7.56 (ddd, $^3J = 8.3$ Hz, $^4J = 1.5$ Hz, 1H, $H_{arom.}$), 7.69–7.77 (m, 2H, $H_{arom.}$), 9.26 (s, 1H, NH) 357.0 [41%, $M^{+\bullet}$], 202.3 [100%, $M^{+\bullet} - SO_2C_6H_4CH_3$], 91.1 (41%, $C_7H_7^+$)
4b	134	3240 (N–H), 1620 (C=O), 1350, 1180 (SO_2–N)	7.04–7.10 (m, 4H, $H_{arom.}$), 7.22 (ddd, $^3J = 7.8$ Hz, $^3J = 7.3$ Hz, $^4J = 1.0$ Hz, 1H, $H_{arom.}$), 7.48 (d, $^3J = 8.3$ Hz, 2H, BB′), 7.58 (ddd, $^3J = 7.8$ Hz, $^3J = 7.3$ Hz, $^4J = 1.5$ Hz, 1H, $H_{arom.}$), 7.72–7.78 (m, 2H, $H_{arom.}$), 9.22 (s, 1H, NH) 377.8 [27%, $M^{+\bullet}$], 202.4 [100%, $M^{+\bullet} - SO_2C_6H_4Cl$], 111.2 (35%, $C_4H_3SCO^+$)
5	100 (99–101 [23])	3260 (N–H), 1650 (C=O), 1330, 1150 (SO_2–N)	3.04 (s, 3H, CH_3), 7.09 (s, 1H, NH), 7.42–7.65 (m, 7H, $H_{arom.}$), 7.77–7.82 (m, 2H, $H_{arom.}$) 275.5 [96%, $M^{+\bullet}$], 196.4 [27%, $M^{+\bullet} - SO_2CH_3$], 105.1 (100%, $C_6H_5CO^+$), 77.4 (70%, $C_6H_5^+$)
6a	118	3300 (N–H), 1670 (C=O), 1330, 1170 (SO_2–N)	2.35 (s, 3H, CH_3), 7.18–7.70 (m, 14H, $H_{arom.}$ and NH) 351.7 [38%, $M^{+\bullet}$], 105.7 (32%, $C_6H_5CO^+$), 91.6 (80%, $C_7H_7^+$), 84.3 (100%), 77.3 (32%, $C_6H_5^+$), 64.6 (21%, SO_2^+)
6b	130	3220 (N–H), 1645 (C=O), 1350, 1170 (SO_2–N)	7.36–7.71 (m, 19H, $H_{arom.}$ and NH) 371.5 [79%, $M^{+\bullet}$], 178.2 (83%), 105.0 (100%, $C_6H_5CO^+$), 77.4 (68%, $C_6H_5^+$)
7	137 (145–147 [24])	3230 (N–H), 1645 (C=O), 1320, 1150 (SO_2–N)	3.12 (s, 3H, CH_3), 7.32 (d, $^3J = 8.6$ Hz, 2H, AA′), 7.41 (s, 1H, NH), 7.46–7.51 (m, 2H, $H_{arom.}$), 7.60 (dddd, $^3J = 7.4$ Hz, $^4J = 1.3$ Hz, 1H, $benzoyl_{H\text{-}4}$), 7.75–7.78 (m, 2H, $H_{arom.}$), 7.83 (d, $^3J = 8.6$ Hz, 2H, BB′) 274.9 [58%, $M^{+\bullet}$], 197.9 [23%, $M^{+\bullet} - C_6H_5$], 105.1 (33%, $C_6H_5CO^+$), 79.3 (70%, $SO_2CH_3^+$)
8a	177 (175 [25])	3230 (N–H), 1645 (C=O), 1350, 1155 (SO_2–N)	2.37 (s, 3H, CH_3), 7.14–7.26 (m, 4H, $H_{arom.}$), 7.40–7.59 (m, 4H, $H_{arom.}$), 7.68–7.77 (m, 6H, $H_{arom.}$ and NH) 351.3 [88%, $M^{+\bullet}$], 274.4 [29%, $M^{+\bullet} - C_6H_5$], 155.0 (46%, $C_6H_4NHSO_2^+$), 105.0 (26%, $C_6H_5CO^+$), 91.1 (100%, $C_7H_7^+$), 77.4 (30%, $C_6H_5^+$)
8b	160	3220 (N–H), 1640 (C=O), 1350 (SO_2–N), 1320, 1150 (SO_2–N)	7.17 (d, $^3J = 8.8$ Hz, 2H, AA′), 7.41–7.61 (m, 6H, $H_{arom.}$), 7.68–7.81 (m, 6H, $H_{arom.}$ and NH) 371.6 [86%, $M^{+\bullet}$], 294.3 [49%, $M^{+\bullet} - C_6H_5$], 196.3 [28%, $M^{+\bullet} - SO_2C_6H_4Cl$], 168.2 (100%), 140.8 (41%, $C_6H_4SO_2^+$), 105.0 (54%, $C_6H_5CO^+$), 77.4 (60%, $C_6H_5^+$)
9	85 (83–84 [26])	3300 (N–H), 1695 (C=O), 1630 (C=O)	2.22 (s, 3H, CH_3), 7.08 (dd, $^3J = 7.9$ Hz, $^4J = 1.2$ Hz, 1H, $H_{arom.}$), 7.46–7.71 (m, 7H, $H_{arom.}$), 8.62 (d, $^3J = 8.3$ Hz, 1H, $H_{arom.}$), 10.81 (s, 1H, NH) 238.9 [44%, $M^{+\bullet}$], 196.0 [100%, $M^{+\bullet} - CH_3CO$]
10a	90	3290 (N–H), 1655 (C=O), 1610 (C=O)	7.13 (ddd, $^3J = 8.0$ Hz, $^3J = 7.3$ Hz, $^4J = 1.2$ Hz, 1H, $H_{arom.}$), 7.47–7.74 (m, 10H, $H_{arom.}$), 8.07 (dd, $^3J = 8.0$ Hz, $^4J = 1.7$ Hz, 2H, $H_{arom.}$), 8.90 (dd, $^3J = 8.6$ Hz, $^4J = 1.0$ Hz, 1H, $H_{arom.}$), 11.98 (s, 1H, NH) 301.1 [26%, $M^{+\bullet}$], 195.9 [39%, $M^{+\bullet} - C_6H_5CO$], 105.1 (100%, $C_6H_5CO^+$), 77.3 (47%, $C_6H_5^+$)

Table 3 (continued).

Compound	m.p. (°C)	IR (KBr)	^{1}H-NMR (200 MHz), δ (ppm), J (Hz)/MS (EI, 70 eV): m/z
10b	81 (75 [27])	3290 (N–H), 1685 (C=O), 1635 (C=O)	2.42 (s, 3H, CH_3), 7.11 (ddd, $^3J = 7.9$ Hz, $^3J = 7.4$ Hz, $^4J = 1.2$ Hz, 1H, $H_{arom.}$), 7.31 (d, $^3J = 7.9$ Hz, 2H, AA′), 7.45–7.74 (m, 7H, $H_{arom.}$), 7.97 (d, $^3J = 8.4$ Hz, 2H, BB′), 8.88–8.91 (m, 1H, $H_{arom.}$), 11.93 (s, 1H, NH) 314.9 [28%, $M^{+\bullet}$], 210.3 [29%, $M^{+\bullet} - C_6H_5CO$], 119.2 (100%, $CH_3C_6H_4CO^+$), 91.3 (43%, $C_7H_7^+$)
10c	104 (103–104 [26])	1690 (C=O), 1625 (C=O)	7.12 (dd, $^3J = 7.8$ Hz, $^3J = 7.3$ Hz, 1H, $H_{arom.}$), 7.45–7.72 (m, 9H, $H_{arom.}$), 8.02 (d, $^3J = 8.3$ Hz, 2H, BB′), 8.83–8.87 (m, 1H, $H_{arom.}$), 12.00 (s, 1H, NH) 335.0 [22%, $M^{+\bullet}$], 230.4 [35%, $M^{+\bullet} - C_6H_5CO$], 139.3 (100%, $ClC_6H_4CO^+$), 111.3 (48%, $C_6H_4Cl^+$)
11a	136	3230 (N–H), 1650 (C=O)	7.16–7.23 (m, 2H, $H_{arom.}$), 7.48–7.59 (m, 3H, $H_{arom.}$), 7.62–7.68 (m, 2H, $H_{arom.}$), 7.76 (dd, $^3J = 4.9$ Hz, $^4J = 1.1$ Hz, 1H, $H_{arom.}$), 7.90 (dd, $^3J = 7.9$ Hz, $^4J = 1.7$ Hz, 1H, $H_{arom.}$), 8.01–8.04 (m, 2H, $H_{arom.}$), 8.80 (dd, $^3J = 8.4$ Hz, $^4J = 0.7$ Hz, 1H, $H_{arom.}$), 11.39 (s, 1H, NH) 306.4 [19%, $M^{+\bullet}$], 195.7 [42%, $M^{+\bullet} - C_4H_3SCO$], 107.7 (100%, $C_6H_5CO^+$), 76.9 (51%, $C_6H_5^+$)
11b	141	3280 (N–H), 1650 (C=O)	2.42 (s, 3H, CH_3), 7.16–7.21 (m, 2H, $H_{arom.}$), 7.30 (d, $^3J = 8.1$ Hz, 2H, AA′), 7.61–7.67 (m, 2H, $H_{arom.}$), 7.76 (dd, $^3J = 5.0$ Hz, $^4J = 1.1$ Hz, 1H, thiophen), 7.87–7.93 (m, 3H, BB′ and thiophen), 8.79 (dd, $^3J = 8.5$ Hz, $^4J = 0.8$ Hz, 1H, thiophen), 11.34 (s, 1H, NH) 320.6 [31%, $M^{+\bullet}$], 209.9 [33%, $M^{+\bullet} - C_4H_3SCO$], 118.7 (100%, $CH_3C_6H_4CO^+$), 90.8 (67%, $C_7H_7^+$)
11c	93	3330 (N–H); 1675 (C=O), 1620 (C=O)	7.15–7.24 (m, 3H, $H_{arom.}$), 7.45 (d, $^3J = 8.3$ Hz, 2H, AA′), 7.61–7.78 (m, 3H, $H_{arom.}$), 7.88–7.97 (m, 3H, BB′ and $H_{arom.}$), 8.75 (d, $^3J = 8.3$ Hz, 1H, $H_{arom.}$), 11.42 (s, 1H, NH) 341.6 [16%, $M^{+\bullet}$], 230.4 [28%, $M^{+\bullet} - C_4H_3SCO$], 202.4 [11%, $M^{+\bullet} - COC_6H_4Cl$], 139.3 (100%, $ClC_6H_4CO^+$), 111.2 (84%, $C_4H_3SCO^+$)
12a	125	3290 (N–H), 1630 (C=O)	7.42–7.61 (m, 8H, $H_{arom.}$), 7.78 (m, 2H, $H_{arom.}$), 7.87 (m, 2H, $H_{arom.}$), 7.94 (dd, $^4J = 1.7$ Hz, 1H, $H_{arom.}$), 8.12 (ddd, $^3J = 8.3$ Hz, $^4J = 1.7$ Hz, 1H, $H_{arom.}$), 8.26 (s, 1H, NH) 300.9 [28%, $M^{+\bullet}$], 105.1 (100%, $C_6H_5CO^+$), 77.2 (34%, $C_6H_5^+$)
12b	112	3310 (N–H), 1635 (C=O)	2.41 (s, 3H, CH_3), 7.25 (d, $^3J = 8.1$ Hz, 2H, AA′), 7.44–7.61 (m, 5H, $H_{arom.}$), 7.76–7.80 (m, 4H, $H_{arom.}$), 7.92 (dd, $^4J = 1.7$ Hz, 1H, $H_{arom.}$), 8.11 (ddd, $^3J = 7.9$ Hz, $^4J = 1.8$ Hz, 1H, $H_{arom.}$), 8.16 (s, 1H, NH) 314.9 [31%, $M^{+\bullet}$], 119.0 (100%, $CH_3C_6H_4CO^+$), 91.0 (86%, $C_7H_7^+$)
12c	135	3290 (N–H), 1625 (C=O)	7.40 (d, $^3J = 8.6$ Hz, 2H, AA′), 7.43–7.49 (m, 3H, $H_{arom.}$), 7.52 (ddd, $^3J = 7.6$ Hz, $^4J = 1.4$ Hz, 1H, $H_{arom.}$), 7.59 (dddd, $^3J = 7.6$ Hz, $^4J = 1.3$ Hz, 1H, $H_{arom.}$), 7.74–7.77 (m, 2H, $H_{arom.}$), 7.82 (d, $^3J = 8.6$ Hz, 2H, BB′), 7.95 (dd, $^4J = 1.7$ Hz, 1H, $H_{arom.}$), 8.12 (ddd, $^3J = 7.9$ Hz, $^4J = 1.8$ Hz, 1H, $H_{arom.}$), 8.34 (s, 1H, NH) 334.3 [31%, $M^{+\bullet}$], 138.6 (100%, $ClC_6H_4CO^+$), 110.9 (36%, $ClC_6H_4^+$)
13a	150	3330 (N–H), 1630 (C=O)	7.45–7.52 (m, 4H, $H_{arom.}$), 7.55–7.62 (m, 2H, $H_{arom.}$), 7.76–7.91 (m, 8H, $H_{arom.}$), 8.15 (s, 1H, NH) 300.9 [39%, $M^{+\bullet}$], 105.0 (100%, $C_6H_5CO^+$), 77.3 (43%, $C_6H_5^+$)
13b	179	3320 (N–H), 1640 (C=O)	2.42 (s, 3H, CH_3), 7.28 (d, $^3J = 8.1$ Hz, 2H, AA′), 7.45–7.50 (m, 2H, $H_{arom.}$), 7.58 (ddd, $^3J = 7.4$ Hz, $^4J = 1.4$ Hz, 1H, $H_{arom.}$), 7.76–7.80 (m, 6H, $H_{arom.}$), 7.85 (dd, $^3J = 8.8$ Hz, 2H, BB′), 8.15 (s, 1H, NH) 314.9 [59%, $M^{+\bullet}$], 119.1 (100%, $CH_3C_6H_4CO^+$), 91.1 (29%, $C_7H_7^+$)
13c	163	3280 (N–H), 1650 (C=O)	7.46–7.51 (m, 4H, AA′ and AA′), 7.59 (dddd, $^3J = 7.4$ Hz, $^4J = 1.3$ Hz, 1H, $H_{arom.}$), 7.76–7.79 (m, 4H, $H_{arom.}$), 7.83–7.88 (m, 4H, BB′ and BB′), 8.05 (s, 1H, NH) 334.4 [18%, $M^{+\bullet}$], 138.7 (100%, $ClC_6H_4CO^+$), 110.9 (30%, $ClC_6H_4^+$)
14	108 (105–107 [28])	3150–3000 (N–H), 1655 (C=O)	2.67 (s, 3H, CH_3CO), 3.06 (s, 3H, SO_2CH_3), 7.15 (ddd, $^3J = 7.6$ Hz, $^4J = 1.2$ Hz, 1H, Ar), 7.56 (ddd, $^3J = 7.6$ Hz, $^4J = 1.7$ Hz, 1H, Ar), 7.75 (dd, $^3J = 8.3$ Hz, $^4J = 1.0$ Hz, 1H, Ar), 7.93 (dd, $^3J = 7.9$ Hz, $^4J = 1.4$ Hz, 1H, Ar), 11.34 (s, 1H, NH) 212.9 [41%, $M^{+\bullet}$], 198.1 [23%, $M^{+\bullet} - CH_3$], 134.1 [100%, $M^{+\bullet} - SO_2CH_3$], 118.8 [43%, $M^{+\bullet} - NHSO_2CH_3$], 106.0 (56%)

Table 3 (continued).

Compound	m.p. (°C)	IR (KBr)	^{1}H-NMR (200 MHz), δ (ppm), J (Hz)/MS (EI, 70 eV): m/z
15	179	3260 (N–H), 1685 (C=O)	3.12 (s, 3H, CH_3), 7.18–7.64 (m, 7H, Ar), 9.29 (s, 1H, NH) 273.0 [84%, $M^{+\cdot}$], 194.8 [100%, $M^{+\cdot}-SO_2CH_3$], 166.9 (23%), 138.8 (29%)
16	129	3180 (N–H), 1660 (C=O), 1325, 1160 (SO_2–N)	2.87 (s, 3H, SO_2CH_3), 3.60 (s, 3H, OCH_3), 6.79 (d, $^3J = 8.3$ Hz, 1H, Ar), 7.31–7.75 (m, 8H, Ar and NH) 304.6 [30%, $M^{+\cdot}$], 225.6 [100%, $M^{+\cdot}-SO_2CH_3$], 210.6 [89%, $M^{+\cdot}-SO_2CH_3$ u. $-CH_3$], 148.6 (37%), 104.9 (49%, $C_6H_5CO^+$), 76.9 (45%, $C_6H_5^+$)
17	128	1670 (C=O), 1340, 1170 (SO_2–N)	2.78 (s, 3H, CH_3), 3.17 (s, 3H, CH_3), 7.39–7.59 (m, 7H, Ar), 7.77–7.81 (m, 2H, Ar) 289.2 [3%, $M^{+\cdot}$], 209.9 [100%, $M^{+\cdot}-SO_2CH_3$], 132.0 (23%), 104.9 (10%, $C_6H_5CO^+$), 91.0 (13%, $C_6H_4NCH_3^+$), 77.3 (26%, $C_6H_5^+$)
18	121	3250 (N–H), 1385, 1155 (SO_2–N)	2.54 (s, 3H, CH_3), 3.32–3.51 (m, 4H, CH_2CH_2), 7.01 (s, 1H, NH), 7.08 7.17 (m, 1H, Ar), 7.28–7.38 (m, 4H, Ar), 7.53–7.60 (m, 2H, Ar), 7.68–7.73 (m, 1H, Ar), 7.82–7.87 (m, 1H, Ar) 350.7 [25%, $M^{+\cdot}$], 289.9 [20%, $M^{+\cdot}-SCH_2CH_2$], 272.2 [20%, $M^{+\cdot}-SO_2CH_3$], 243.9 (100%), 211.8 (43%), 92.3 (37%, $SCH_2CH_2S^+$)
19	115	3440 (O–H), 3250 (N–H), 1330, 1150 (SO_2–N)	DMSO-d_6, 2.59 (s, 3H, CH_3), 6.09 (s, 1H, CH), 6.40 (s, 1H, OH), 7.16–7.42 (m, 9H, Ar), 8.96(s, 1H, NH) 277.0 [13%, $M^{+\cdot}$], 198.0 [100%, $M^{+\cdot}-SO_2CH_3$], 180.0 (98%), 120.2 (35%), 104.9 (31%, $C_6H_5CO^+$), 77.4 (22%, $C_6H_4^+$)
20	117	3290 (N–H), 1310, 1150 (SO_2–N)	2.59 (s, 3H, CH_3), 4.01 (s, 2H, CH_2), 6.20 (s, 1H, NH), 7.13–7.33 (m, 8H, Ar), 7.50–7.54 (m, 1H, Ar) 261.6 [22%, $M^{+\cdot}$], 182.4 (100%, $C_6H_5CH_2C_6H_4NH^+$)

6.3. General procedure for the preparation of carbonyl chlorides (Method B)

6.3.1. Carbonyl chlorides via $SOCl_2$

The HCO_3 was refluxed with an excess of $SOCl_2$ for 3 h. The excess $SOCl_2$ was distilled at a water jet pump and the residue dissolved with CH_2Cl_2 and washed briefly with ice-water. The organic layer was separated, washed three times with water, Na_2CO_3 and water and finally dried with Na_2SO_4. The solvent was evaporated under reduced pressure to yield the crude product, which was not usually purified any further.

6.3.2. Carbonyl chlorides via PCl_5

To a cooled (ice bath) solution of HCO_3 in $CH_2Cl_2{\cdot}PCl_5$ was added. The ice bath was removed and the mixture was stirred under reflux for 2 h. For Friedel-Crafts-acylation the mixture was not further purified.

6.4. General procedure for the Friedel-Crafts-reaction (Method C)

On an ice bath, dry $AlCl_3$ was suspended in dry CH_2Cl_2 and stirred vigorously. To this mixture, a solution of the carbonyl chloride or alkyl halide in CH_2Cl_2 and subsequently the aromatic compound (solved in CH_2Cl_2) was added dropwise. After stirring over night at r.t. the complex was hydrolysed with crushed ice and acidified with diluted HCl. The organic layer was separated, washed three times with water, Na_2CO_3 and water and finally dried with Na_2SO_4. The solvent was evaporated under reduced pressure to yield the crude product, which was usually purified by CC.

*6.5. N-(2-Benzoylphenyl)methanesulphonamide (**1a**)*

To a stirred solution of 1.97 g (10 mmol) 2-aminophenyl-phenylmethanone and 1.19 g (15 mmol) pyridine in 100 mL dry CH_2Cl_2 1.38 g (12 mmol) methanesulphonyl chloride were added dropwise. The solution was stirred for 3 h at r.t. before it was hydrolysed with the equivalent amount of water. The organic layer was separated, washed three times with water, Na_2CO_3 and water and finally dried with Na_2SO_4. The solvent was evaporated under reduced pressure yielding a yellow oil. CC (PE–EE = 1:1) yielded yellow crystals (1.39 g, 51%). Anal. Calc. for $C_{14}H_{13}NO_3S$: C, 61.08; H, 4.76. Found: C, 60.63; H, 5.10%; N.

*6.6. 2-Methylsulphonylamidobenzoic acid (**VII**)*

To a cooled solution (ice bath) of 1.36 g (10 mmol) 2-amino-benzoic acid in 30 mL saturated aq. Na_2CO_3, methanesulphonyl chloride (1.38 g, 12 mmol) were added. The solution was stirred over night and allowed to warm up to r.t. The solution was acidified with concd. HCl and the precipitate collected and dried. The precipitate was used without any further purification.

Yield: 1.76 g (82%), m.p. 183 °C (Ref. [33]: 189–190 °C).

6.7. N-[2-(4-Methylbenzoyl)phenyl]methanesulphonamide (**1b**)

1.08 g **VII** (5 mmol) was transformed according to Method B. Ten millilitres $SOCl_2$ were added to carbonyl chloride, and subsequently reacted with 0.92 g $C_6H_5CH_3$ (10 mmol) and 0.80 g $AlCl_3$ (6 mmol) in 30 mL CH_2Cl_2 (Method C). The crude product was recrystallised with PE–CH_2Cl_2 yielding 0.93 g (64%) of white crystals. Anal. ($C_{15}H_{15}NO_3S$): C, H, N, S.

6.8. N-[2-(4-Methylsulphanylbenzoyl)-phenyl]methanesulphonamide (**1c**)

Compound **VII** (1.61 g, 7.5 mmol) was transformed according to Method B with 15 mL $SOCl_2$ to carbonyl chloride, which was subsequently reacted with 2.33 g 1-methylsulphanylbenzene (18.8 mmol) and 1.20 g $AlCl_3$ (9.0 mmol) in 50 mL CH_2Cl_2 (Method C). CC of the crude product (PE–EE = 2:1; $R_f = 0.33$) yielded 0.90 g (38%) of yellow crystals. Anal. ($C_{15}H_{15}NO_3S_2$): C, H, N.

6.9. 2-Aminophenyl-4-phenylphenylmethanone (**VIII**)

A stirred mixture of 7.71 g 1-phenylbenzene (50 mmol), 1.63 g isatoic anhydride (10 mmol) and 6.0 g $AlCl_3$ (45 mmol) was melted for 8 h at 110 °C. The resulting black product was dissolved in 300 mL CH_2Cl_2. The organic layer was separated, washed three times with water, Na_2CO_3 and water and finally dried with Na_2SO_4. CC of the crude product (PE–CH_2Cl_2 = 4:1; $R_f = 0.36$) yielded 1.01 g (37%) of a yellow liquid.

6.10. N-[2-(2-Phenylbenzoyl)phenyl]methanesulphonamide (**1d**)

Compound **VIII** (0.50 g, 1.83 mmol) was reacted with 0.29 g pyridine (3.66 mmol) and 0.25 g methanesulphonyl chloride (2.20 mmol) in 30 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–CH_2Cl_2 = 3:1; $R_f = 0.27$) yielded 0.24 g (38%) of yellow crystals. Anal. ($C_{20}H_{17}NO_3S$): C, H, N, S.

6.11. [4-(tert-Butyl)phenyl](2-nitrophenyl)-methanone (**IX**)

2-Nitro-1-benzenecarbonyl chloride (3.73 g, 22 mmol) were reacted with 2.68 g 1-(*tert*-butyl)benzene (20 mmol) and 5.33 g $AlCl_3$ (40 mmol) in 30 mL CH_2Cl_2 (Method C). CC of the crude product (PE–EE = 4:1; $R_f = 0.50$) yielded 2.11 g (37%) of white crystals (m.p. 101 °C).

6.12. (2-Aminophenyl)[4-(tert-butyl)phenyl]-methanone (**X**)

Compound **IX** (1.50 g, 5.30 mmol) in 50 mL MeOH were hydrogenated with 0.10 g Pd–C (10%) and H_2 (5 bar) at r.t. for 6 h. The mixture was filtered over celite® and the solvent evaporated under reduced pressure. CC of the crude product (PE–EE = 8:1; $R_f = 0.24$) yielded 1.02 g (76%) of yellow crystals (m.p. 120 °C).

6.13. (N-{2-[(4-tert-Butyl)benzoyl]phenyl}-methanesulphonamide (**1e**)

Compound **X** (0.76 g, 3.0 mmol) were reacted with 0.45 g pyridine (6.0 mmol) and 0.52 g methanesulphonyl chloride (4.50 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 5:1; $R_f = 0.20$) yielded 0.36 g (36%) of yellow solid. Anal. ($C_{18}H_{21}NO_3S$): C, H, N.

6.14. 2-Benzoyl-1-phenylsulphonamidobenzene (**2a**)

2-Aminophenyl-phenylmethanone (1.97 g, 10.0 mmol) were reacted with 1.19 g pyridine (15.0 mmol) and 1.69 g 1-benzenesulphonyl chloride (12.0 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 4:1; $R_f = 0.42$) yielded 2.13 g (63%) of yellow crystals. Anal. ($C_{19}H_{15}NO_3S$): C, H, N, S.

6.15. 2-Benzoyl-1-(4-methylphenylsulphonamido)-benzene (**2b**)

2-Aminophenyl-phenylmethanone (3.95 g, 20.0 mmol) were reacted with 2.37 g pyridine (30.0 mmol) and 4.19 g 4-methyl-1-benzenesulphonyl chloride (22.0 mmol) in 100 mL CH_2Cl_2 according to Method A. The crude product was recrystallised with PE–CH_2Cl_2 yielding 6.15 g (88%) of yellow crystals. Anal. ($C_{20}H_{17}NO_3S$): C, H, N.

6.16. 2-Benzoyl-1-(4-chlorophenylsulphonamido)-benzene (**2c**)

2-Aminophenyl-phenylmethanone (1.97 g, 10.0 mmol), 1.19 g pyridine (15.0 mmol) and 2.53 g 4-chloro-1-benzenesulphonyl chloride (12.0 mmol) were reacted in 50 mL CH_2Cl_2 according to Method A. The crude product was recrystallised with PE–CH_2Cl_2 yielding 2.79 g (75%) of yellow crystals. Anal. ($C_{19}H_{14}ClNO_3S$): C, H, N, Cl, S.

6.17. 2-Benzoyl-1-(4-methoxy-phenylsulphonamido)-benzene (**2d**)

2-Aminophenyl-phenylmethanone (1.97 g, 10.0 mmol) were reacted with 1.19 g pyridine (15.0 mmol) and 1.69 g 4-methoxy-1-benzenesulphonyl chloride (12.0 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 2:1; $R_f = 0.40$) yielded 2.06 g (56%) of yellow crystals. Anal. ($C_{20}H_{17}NO_4S$): C, H, N.

6.18. 2-Benzoyl-1-[4-(tert-butyl)phenylsulphonamido]-benzene (**2e**)

2-Aminophenyl-phenylmethanone (1.97 g, 10.0 mmol) were reacted with 1.19 g pyridine (15.0 mmol) and 2.79 g 4-*tert*-butyl-1-benzenesulphonyl chloride (12.0 mmol) in 50 mL CH_2Cl_2 according to Method A. The crude product was recrystallised with PE–Et_2NH 9:1 (50 mL) yielding the Et_2NH salt which was dissolved in CH_2Cl_2 and washed with diluted HCl. The organic layer was separated, washed twice with water and dried with Na_2SO_4. The product was recrystallised with PE–CH_2Cl_2 yielding 1.76 g (48%) of yellow crystals. Anal. Calc. for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89. Found: C, 70.95; H, 5.41%; N.

6.19. N1-(Benzoylphenyl)-3,5-di(trifluoromethyl)-1-benzenesulphonamid (**2f**)

2-Aminophenyl-phenylmethanone (0.33 g, 1.6 mmol) were reacted with 0.20 g pyridine (2.50 mmol) and 0.63 g 3,5-bis(trifluoromethyl)benzenesulphonyl chloride (2.0 mmol) in 20 mL CH_2Cl_2 according to Method A. The crude product was recrystallised with PE–CH_2Cl_2 yielding 0.39 g (52%) of yellow solid. Anal. ($C_{21}H_{13}F_6NO_3S$): C, H, N, S.

6.20. N2-(2-Benzoylphenyl)-2-naphthalenesulphonamide (**2g**)

2-Aminophenyl-phenylmethanone (0.99 g, 5.0 mmol) were reacted with 0.59 g pyridine (7.5 mmol) and 1.36 g 2-naphthalenesulphonyl chloride (6.0 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 2:1; $R_f = 0.40$) yielded 1.05 g (54%) of colourless crystals. Anal. ($C_{23}H_{17}NO_3S$) C, H, N.

6.21. N2-(2-Benzoylphenyl)-2-thiophenesulphonamide (**2h**)

2-Aminophenyl-phenylmethanone (0.99 g, 5.0 mmol) were reacted with 0.59 g pyridine (7.5 mmol) and 1.07 g 2-thiophenesulphonyl chloride (6.0 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–CH_2Cl_2 = 4:1; $R_f = 0.23$) yielded 1.15 g (68%) of white solid. Anal. ($C_{17}H_{13}NO_3S_2$): C, H, N.

6.22. (4-Methylphenyl)(2-nitrophenyl)methanone (**XI**)

2-Nitro-1-benzenecarbonyl chloride (3.73 g, 22 mmol) were reacted with 1.84 g $C_6H_5CH_3$ (20 mmol) and 5.33 g $AlCl_3$ (40 mmol) in 50 mL CH_2Cl_2 (Method C). The crude product was recrystallised with PE–CH_2Cl_2 yielding 2.88 g (60%) of yellow crystals [m.p. 154 °C (Ref. [34]: 155 °C)].

6.23. (2-Aminophenyl)(4-methylphenyl)methanone (**XII**)

Compound **XI** (0.72 g, 3.0 mmol) in 50 mL MeOH were hydrogenated with 0.08 g Pd–C (10%) and H_2 (5 bar) at r.t. for 6 h. The mixture was filtered over celite® and the solvent evaporated under reduced pressure to yield a yellow liquid (0.63 g, 99%; m.p. Ref. [35]: 82–83 °C). The crude product was used without further purification.

6.24. N1-[2-(4-Methylbenzoyl)phenyl]-4-methyl-1-benzenesulphonamide (**2i**)

Compound **XII** (0.68 g, 3.0 mmol) were reacted with 0.48 g pyridine (6.0 mmol) and 0.88 g 4-methyl-1-benzenesulphonyl chloride (4.5 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–CH_2Cl_2 = 4:1; $R_f = 0.37$) yielded 0.67 g (56%) of white solid. Anal. ($C_{21}H_{19}NO_3S$): C, H, N.

6.25. N1-{2-[4-(tert-Butyl)benzoyl]phenyl}-4-methyl-1-benzenesulphonamide (**2j**)

Compound **X** (0.63 g, 2.5 mmol) were reacted with 0.37 g pyridine (5.0 mmol) and 0.72 g 4-methyl-1-benzenesulphonyl chloride (3.8 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 5:1; $R_f = 0.25$) yielded 0.42 g (41%) of white solid. Anal. ($C_{24}H_{25}NO_3S$): C, H, N.

6.26. N-[2-(2-Thienylcarbonyl)phenyl]methanesulphonamide (**3**)

(2-Aminophenyl)(2-thienyl)methanone (0.45 g, 2.2 mmol) (synthesised according to the procedure described by Hunziker et al. [17]) were reacted with 0.26 g pyridine (3.3 mmol) and 0.30 g methanesulphonyl chloride (2.64 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 2:1; $R_f = 0.20$) yielded 0.25 g (41%) of a yellow liquid. Anal. Calc. for $C_{12}H_{11}NO_3S_2$: C, 51.23, H and N, 4.98. Found: C, 52.28; H and N, 4.41%.

*6.27. N1[2-(2-Thienylcarbonyl)phenyl]-4-methyl-1-benzenesulphonamide (**4a**)*

(2-Aminophenyl)(2-thienyl)methanone (0.45 g, 2.2 mmol) (synthesised according to the procedure described by Hunziker et al. [17]) were reacted with 0.26 g pyridine (3.3 mmol) and 0.50 g 4-methyl-1-benzenesulphonyl chloride (2.64 mol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 4:1; $R_f = 0.17$) yielded 0.48 g (61%) of yellow crystals. Anal. ($C_{18}H_{15}NO_3S_2$): C, H, N.

*6.28. N1-[2-(2-Thienylcarbonyl)phenyl]-4-chloro-1-benzenesulphonamide (**4b**)*

(2-Aminophenyl)(2-thienyl)methanone (0.45 g, 2.2 mmol) (synthesised according to the procedure described by Hunziker et al. [17]) were reacted with 0.26 g pyridine (3.3 mmol) and 0.56 g 4-chloro-1-benzenesulphonyl chloride (2.64 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 4:1; $R_f = 0.33$) yielded 0.79 g (75%) of yellow crystals. Anal. ($C_{17}H_{12}ClNO_3S_2$): C, H, N.

*6.29. N-(3-Benzoylphenyl)methanesulphonamide (**5**)*

3-Aminophenyl-phenylmethanone (0.99 g, 5.0 mmol) were reacted with 0.59 g pyridine (7.5 mmol) and 0.69 g methanesulphonyl chloride (6.0 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 1:1; $R_f = 0.56$) yielded 0.99 g (72%) of white crystals. Anal. ($C_{14}H_{13}NO_3S$): C, H, N.

*6.30. 3-Benzoyl-1-(4-methylphenylsulphonamido)benzol (**6a**)*

3-Aminophenyl-phenylmethanone (0.99 g, 5.0 mmol) were reacted with 0.59 g pyridine (7.5 mmol) and 1.14 g 4-methyl-1-benzenesulphonyl chloride (6.0 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 2:1; $R_f = 0.38$) yielded 1.19 g (68 %) of white crystals. Anal. ($C_{20}H_{17}NO_3S$): C, H, N.

*6.31. 3-Benzoyl-1-(4-chlorophenylsulphonamido)benzene (**6b**)*

3-Aminophenyl-phenylmethanone (0.99 g, 5.0 mmol) were reacted with 0.59 g pyridine (7.5 mmol) and 1.27 g 4-chloro-1-benzenesulphonyl chloride (6.0 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 3:1; $R_f = 0.22$) yielded 1.50 g (80%) of a white solid. Anal. ($C_{19}H_{14}ClNO_3S$): C, H, N.

*6.32. N-(4-Benzoylphenyl)methanesulphonamide (**7**)*

4-Aminophenyl-phenylmethanone (1.97 g, 10.0 mmol) were reacted with 1.19 g pyridine (15.0 mmol) and 1.38 g methanesulphonyl chloride (12.0 mmol) in 100 mL CH_2Cl_2 according to Method A. The crude product was recrystallised with PE–CH_2Cl_2 yielding 2.09 g (76%) of pale pink crystals. Anal. Calc. for $C_{14}H_{13}NO_3S$: C, 61.07. Found: C, 60.61%; H, N.

*6.33. N1-(4-Benzoylphenyl)-4-methyl-1-benenelsulphonamide (**8a**)*

4-Aminophenyl-phenylmethanone (0.99 g, 5.0 mmol) were reacted with 0.59 g pyridine (7.5 mmol) and 1.14 g 4-methyl-1-benzenesulphonyl chloride (6.0 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 3:1; $R_f = 0.22$) yielded 1.63 g (93%) of a white solid. Anal. Calc. for $C_{20}H_{17}NO_3S$: C, 68.90. Found: C, 68.27%; H, N.

*6.34. 4-Benzoyl-1-(4-chlorophenylsulphonamido)-benzene (**8b**)*

4-Aminophenyl-phenylmethanone (0.99 g, 5.0 mmol) were reacted with 0.59 g pyridine (7.5 mmol) and 1.27 g 4-chloro-1-benzenesulphonyl chloride (6.0 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 5:2; $R_f = 0.29$) yielded 1.73 g (93%) of white crystals. Anal. ($C_{19}H_{14}ClNO_3S$): C, H, N.

*6.35. N1-(2-Benzoylphenyl)acetamide (**9**)*

2-Aminophenyl-phenylmethanone (1.97 g, 10.0 mmol) were reacted with 1.19 g pyridine (15.0 mmol) and 0.94 g ethanoyl chloride (12.0 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 3:1; $R_f = 0.47$) yielded 1.46 g (61%) of white crystals. Anal. ($C_{15}H_{13}NO_2$): C, H, N.

*6.36. 2-Benzoyl-1-phenylcarboxamidobenzene (**10a**)*

2-Aminophenyl-phenylmethanone (0.99 g, 5.0 mmol) were reacted with 0.59 g pyridine (7.5 mmol) and 0.84 g 1-benzenecarbonyl chloride (6.0 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 6:1; $R_f = 0.27$) yielded 1.56 g (99%) of a white solid. Anal. ($C_{20}H_{15}NO_2$): C, H, N.

*6.37. N1-(2-Benzoylphenyl)-4-methylbenzamide (**10b**)*

2-Aminophenyl-phenylmethanone (1.48 g, 7.5 mmol) were reacted with 1.58 g pyridine (20 mmol) and 1.55 g 4-methyl-1-benzenecarbonyl chloride (10.0 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 8:1; $R_f = 0.25$) yielded 1.59 g (67%) of yellow crystals. Anal. ($C_{20}H_{15}NO_2$): C, H, N.

6.38. N1-(2-Benzoylphenyl)-4-chlorobenzamide ***(10c)***

2-Aminophenyl-phenylmethanone (0.99 g, 5 mmol) were reacted with 0.59 g pyridine (7.5 mmol) and 1.05 g 4-chloro-1-benzenecarbonyl chloride (6.0 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 4:1; $R_f = 0.33$) yielded 1.08 g (64%) of a yellow solid. Anal. ($C_{20}H_{14}ClNO_2$): C, H, N.

6.39. 1-Phenylcarboxyamido-2-(2-thienylcarbonyl)-benzene ***(11a)***

(2-Aminophenyl)(2-thienyl)methanone (0.61 g, 3.0 mmol) (synthesised according to the procedure described by Hunziker et al. [17]) were reacted with 0.48 g pyridine (6.0 mmol) and 0.63 g benzenecarbonyl chloride (4.5 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 4:1; $R_f = 0.36$) gave 0.84 g (91%) of yellow crystals. Anal. ($C_{18}H_{13}NO_2S$): C, H, N.

6.40. 1-(4-Methylphenylcarboxyamido)-2-(2-thienylcarbonyl)benzene ***(11b)***

(2-Aminophenyl)(2-thienyl)methanone (0.61 g, 3.0 mmol) (synthesised according to the procedure described by Hunziker et al. [17] were reacted with 0.48 g pyridine (6.0 mmol) and 0.70 g 4-methyl-1-benzenecarbonyl chloride (4.5 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 4:1; $R_f = 0.34$) yielded 0.86 g (89%) of yellow crystals. Anal. ($C_{19}H_{15}NO_2S$): C, H, N.

6.41. N1-[2-(2-Thienylcarbonyl)phenyl]-4-chloro-benzamide ***(11c)***

(2-Aminophenyl)(2-thienyl)methanone (0.48 g, 2.2 mmol) (synthesised according to the procedure described by Hunziker et al. [17]) were reacted with 0.26 g pyridine (3.3 mmol) and 0.46 g 4-chloro-1-benzenecarbonyl chloride (2.64 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–CH_2Cl_2 = 1:3; $R_f = 0.50$) yielded 0.46 g (61%) of a yellow solid. Anal. Calc. for $C_{18}H_{12}ClNO_2S$: C, 63.25. Found: C, 62.79%; H, N.

6.42. 3-Benzoyl-1-phenylcarboxamidobenzene ***(12a)***

3-Aminophenyl-phenylmethanone (0.59 g, 3.0 mmol) were reacted with 0.36 g pyridine (4.5 mmol) and 0.51 g 1-benzenecarbonyl chloride (3.6 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 2:1; $R_f = 0.48$) yielded 0.85 g (94%) of white crystals. Anal. Calc. for $C_{20}H_{15}NO_2$: C, 79.71. Found: C, 79.08%; H, N.

6.43. 3-Benzoyl-1-(4-methylphenylcarboxamido)benzene ***(12b)***

3-Aminophenyl-phenylmethanone (0.59 g, 3.0 mmol) were reacted with 0.36 g pyridine (4.5 mmol) and 0.56 g 4-methyl-1-benzenecarbonyl chloride (3.6 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 2:1; $R_f = 0.60$) yielded 0.86 (91%) of white crystals. Anal. ($C_{21}H_{17}NO_2$): C, H, N.

6.44. 3-Benzoyl-1-(4-chlorophenylcarboxamido)benzene ***(12c)***

3-Aminophenyl-phenylmethanone (0.59 g, 3.0 mmol) were reacted with 0.36 g pyridine (4.5 mmol) and 0.63 g 4-chloro-1-benzenecarbonyl chloride (3.6 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 4:1; $R_f = 0.27$) yielded 0.81 g (81%) of white crystals. Anal. ($C_{20}H_{14}ClNO_2$): C, H, N.

6.45. 4-Benzoyl-1-phenylcarboxamidobenzene ***(13a)***

4-Aminophenyl-phenylmethanone (0.59 g, 3.0 mmol) were reacted with 0.36 g pyridine (4.5 mmol) and 0.51 g 1-benzenecarbonyl chloride (3.6 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 2:1; $R_f = 0.41$) yielded 0.81 g (89%) of white crystals. Anal. ($C_{20}H_{15}NO_2$): C, H, N.

6.46. 4-Benzoyl-1-(4-methylphenylcarboxamido)benzene ***(13b)***

4-Aminophenyl-phenylmethanone (0.59 g, 3.0 mmol) were reacted with 0.36 g pyridine (4.5 mmol) and 0.56 g 4-methyl-1-benzenecarbonyl chloride (3.6 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 2:1; $R_f = 0.58$) yielded 0.72 g (76%) of white crystals. Anal. ($C_{21}H_{17}NO_2$): C, H, N.

6.47. 4-Benzoyl-1-(4-chlorophenylcarboxamido)benzene ***(13c)***

4-Aminophenyl-phenylmethanone (0.59 g, 3.0 mmol) were reacted with 0.36 g pyridine (4.5 mmol) and 0.63 g 4-chloro-1-benzenecarbonyl chloride (3.6 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 2:1; $R_f = 0.49$) yielded 0.84 g (83%) of a white solid. Anal. ($C_{20}H_{14}ClNO_2$): C, H, N.

6.48. N-(2-Acetylphenyl)methanesulphonamide ***(14)***

1-(2-Aminophenyl)-1-ethanone (0.68 g, 5.0 mmol) were reacted with 0.59 g pyridine (7.5 mmol) and 0.69 g methanesulphonyl chloride (6.0 mmol) in 50 mL CH_2Cl_2 according to Method A. The crude product was recrystallised with PE–EE yielding 0.65 g (61%) of white crystals. Anal. ($C_9H_{11}NO_3S$): C, H, N.

6.49. N-(9-Oxo-9H-1-fluorenyl)methanesulphonamide (15)

1-Amino-9*H*-9-fluorenone (0.45 g, 2.30 mmol) were reacted with 0.46 g pyridine (5.8 mmol) and 0.40 g methanesulphonyl chloride (3.45 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 3:1; $R_f = 0.22$) yielded 0.18 g (29%) of an orange solid. Anal. ($C_{14}H_{11}NO_2S$): C, H, N.

6.50. N-(2-Benzoyl-3-methoxyphenyl)methanesulphonamide (16)

(2-Amino-6-methoxyphenyl)(phenyl)methanone (0.80 g, 3.5 mmol) (synthesised according to the procedure described by Walsh [14]) were reacted with 0.42 g pyridine (5.3 mmol) and 0.48 g methanesulphonyl chloride (4.2 mmol) in 50 mL CH_2Cl_2 according to Method A. CC of the crude product (PE–EE = 6:1; $R_f = 0.37$) yielded 0.55 g (51%) of a yellow solid. Anal. ($C_{15}H_{15}NO_4S$) C, H, N.

6.51. N-(2-Benzoylphenyl)-N-methylmethanesulphonamide (17)

Compound **1a** (0.83 g, 3.0 mmol) were dissolved in 30 mL of absolute THF and stirred. To the stirred solution, 0.76 g dimethyl sulphate (6.0 mmol) were added dropwise and the mixture stirred over night. To this mixture were added 50 mL of concd. NH_3 and refluxed for 1 h. The solution was washed three times with 50 mL CH_2Cl_2. The organic layers were collected, dried over Na_2SO_4 and the solvent was evaporated. CC of the crude product (PE–EE = 1:1; $R_f = 0.33$) yielded 0.49 g (56%) of yellow crystals. Anal. ($C_{15}H_{15}NO_2S$): C, H, N.

6.52. N-[2-(2-Phenyl-1,3-dithiolane-2-yl)phenyl]-methanesulphonamide (18)

To a cooled (ice bath) solution of 0.83 g **1a** (3.0 mmol) and 0.57 g 1,2-ethanedithiol (6.0 mmol) in 50 mL CH_2Cl_2, 0.55 g boron trifluoride etherate (4 mmol) were added dropwise. After 30 min the ice bath was removed and the solution stirred over night at r.t. The organic phase was washed with saturated $NaHCO_3$ and subsequently with water. The organic layer was separated dried over Na_2SO_4 and the solvent evaporated. CC of the crude product (PE–EE = 4:1; $R_f = 0.32$) yielded 0.74 g (70%) of white solid. Anal. ($C_{16}H_{17}NO_2S_3$): C, H, N.

6.53. N-[2-Hydroxy(phenyl)methylphenyl]-methanesulphonamide (19)

$LiAlH_4$ (0.046 g, 1.2 mmol) were dissolved in 20 mL absolute THF and stirred. To this suspension a solution of 1.10 g **1a** (4.0 mmol) in 30 mL of absolute THF were added dropwise and the mixture was heated under reflux for 1 h at r.t. The mixture was poured into ice water and acidified with 10% H_2SO_4. The organic layer was separated dried over Na_2SO_4 and the solvent evaporated. The crude product was recrystallised with PE–EE yielding 0.73 g (66%) of white crystals. Anal. ($C_{14}H_{15}NO_3S$): C, H, N.

6.54. N-(2-Benzylphenyl)methanesulphonamide (20)

To a stirred solution of 1.83 g (10 mmol) 2-benzylphenylamine and 2.53 g (25 mmol) Et_3N in 100 mL dry 1,2-dichloroethane, 2.29 g (20 mmol) methanesulphonyl chloride were added dropwise. The solution was refluxed for 10 h before being hydrolysed with the equivalent amount of water. The organic layer was separated, washed three times with water, Na_2CO_3 and water and finally dried with Na_2SO_4. The solvent was evaporated under reduced pressure yielding a yellow oil. CC of the crude product (PE–EE = 4:1; $R_f = 0.18$) yielded 1.22 g (47%) of white crystals. Anal. ($C_{14}H_{15}NO_2S$): C, H, N, S.

Acknowledgements

Financial support by the Fonds der Chemischen Industrie is gratefully acknowledged.

References

[1] J.R. Vane, Nature 231 (1971) 232–235.
[2] M.B. Kimmey, J. Rheumatol. 19 (Suppl. 36) (1992) 68–73.
[3] A. Whelton, J. Clin. Pharmacol. 35 (1995) 454–463.
[4] J.-Y. Fu, J.L. Masferrer, K. Seibert, et al., J. Biol. Chem. 265 (1990) 16737–16740.
[5] J.L. Masferrer, B.S. Zweifel, K. Seibert, et al., J. Clin. Invest. 86 (1990) 1375–1379.
[6] J.L. Masferrer, B.S. Zweifel, P.T. Manning, et al., Proc. Natl. Acad. Sci. USA 91 (1994) 3228–3232.
[7] G. Dannhardt, W. Kiefer, G. Krämer, et al., Eur. J. Med. Chem. 35 (5) (2000) 499–510.
[8] F. Catella-Lawson, B.W. McAdam, et al., J. Pharmacol. Exp. Ther. 289 (1999) 735–741.
[9] (a) G. Dannhardt, S. Laufer, Curr. Med. Chem. 7 (2000) 1101–1112;
(b) G. Dannhardt, W. Kiefer, Eur. J. Med. Chem. 36 (2001) 109–126.
[10] J.L. Wallace, TIPS 20 (1999) 4–6.
[11] J.K. Harrington, J.E. Robertson, D.C. Kvam, et al., J. Med. Chem. 13 (1970) 137.
[12] G.G.I. Moore, J.K. Harrington, J. Med. Chem. 18 (1975) 386–391.
[13] E. Schröder, M. Lehmann, C. Rufer, et al., Eur. J. Med. Chem.-Chim. Ther. 17 (1982) 165–172.
[14] D.B. Walsh, Synthesis (1980) 677–688.
[15] N. Miyachi, Y. Yanagawa, H. Iwasaki, et al., Tetrahedron Lett. 34 (1993) 8267–8270.

[16] R. Guilhemat, M. Pereyre, M. Pétraud, Bull. Soc. Chim. Fr. II (1980) 334–344.
[17] F. Hunziker, R. Fischer, P. Kipfer, et al., Eur. J. Med. Chem.-Chim. Ther. 16 (1981) 391–398.
[18] M. Weyman, W. Pfrengle, D. Schollmeyer, et al., Synthesis (1997) 1151–1160.
[19] Patent, Eli Lilly and Comp., US 3838167, 1974.
[20] F. Ullmann, H. Bleier, Chem. Ber. 35 (1902) 4273–4280.
[21] J. Beger, R. Neumann, K. Gloe, et al., J. Prakt. Chem. 330 (1988) 683–694.
[22] W. Steinkopf, E. Günther, Liebigs Ann. Chem. 522 (1936) 28–34.
[23] R.D. Trepka, J.K. Harrington, J.W. Belisle, J. Org. Chem. 39 (1974) 1094–1098.
[24] Patent, Bristol-Myers, DE 2514809, 1975.
[25] N.R. Ayyangar, R.J. Lahoti, K.V. Srinivasan, et al., Synthesis (1991) 322–324.
[26] A. Fürstner, D.N. Jumbam, Tetrahedron 48 (1992) 5991–6010.
[27] R.R. Schmidt, B. Beitzke, Chem. Ber. 116 (1983) 2115–2135.
[28] R.H. Uloth, J.R. Kirk, W.A. Gould, et al., J. Med. Chem. 9 (1966) 88–97.
[29] G. Dannhardt, L. Flemmer, R.W. Hartmann, et al., Arch. Pharm. Pharm. Med. Chem. 331 (1998) 359–364.
[30] B.L. Fiebich, K. Lieb, M. Busse-Grawitz, et al., J. Neuroimmunol. 67 (1996) 77–81.
[31] J.Y. Gauthier, et al., Bioorg. Med. Chem. Lett. 6 (1996) 87–92.
[32] (a) G. Dannhardt, W. Kiefer, G. Krämer, et al., Eur. J. Med. Chem. 35 (5) (2000) 499–510;
(b) Dannhardt G., unpublished results.
[33] F.M. Menger, C.L. Johnson, Tetrahedron 23 (1967) 19–27.
[34] M. Boetius, H. Römisch, Chem. Ber. 68 (1935) 1924–1932.
[35] D.G. Hawkins, O. Meth-Cohn, J. Chem. Soc. Perkin Trans. I (1983) 2077–2087.