Bioorganic & Medicinal Chemistry 18 (2010) 8076–8084

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Identification of a novel pyrrole derivative endowed with antimycobacterial activity and protection index comparable to that of the current antitubercular drugs streptomycin and rifampin

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ARTICLE INFO

Article history:
Received 10 May 2010
Revised 30 August 2010
Accepted 2 September 2010
Available online 19 September 2010

Keywords:
Cytotoxicity
Pharmacophore model
Protection index
Pyrroles
Tuberculosis

ABSTRACT

A hit optimization procedure based on isosteric and bioisosteric replacement of decorating groups at both the N1 and the C5 phenyl rings of 1,5-diarylpyrroles led to identification of 4-((1-(4-fluorophenyl)-2-methyl-5-(4-(methylthio)phenyl)-1*H*-pyrrol-3-yl)methyl)thiomorpholine that is characterized by a very high activity toward both *Mycobacterium tuberculosis* 103471 and H37Rv strains (MIC values of 0.125 μg/mL), and a safe profile in terms of cytotoxicity (CC_{50} of >128 μg/mL) and protection index (>1000). Antitubercular activity and protection index of the new compound are comparable to those found for the current antitubercular drugs streptomycin and rifampin.

1. Introduction

Tuberculosis (TB) has infected man since the birth of civilization and despite the introduction of TB chemotherapy in the 1950s it has made a dramatic resurgence in the past decades and it still remains a leading infectious disease worldwide.[1] The major factors explaining the explosion in numbers of infections with *Mycobacterium tuberculosis* (MTB) are: (i) the deadly synergy with HIV,[2,3] (ii) the development and spread of multidrug-resistant strains of MTB (MDR-TB),[4–6] resistant to all the first-line drugs, and, (iii) more recently, the emergence of extensively drug resistant MTB strains (XDR-TB),[7,8] also resistant to three or more of the six classes of second-line drugs and untreatable using currently available anti-TB drugs. With this background, there have been no new drugs to treat TB, except fluoroquinolone antibiotics recently introduced,[9] in the last 40 years. This reflects the inherent difficulties in developing and clinical testing new agents as well as the lack of pharmaceutical industry research in the area.[10] The priority is the development of a new agent that will shorten the duration of chemotherapy from the current 6–8 months to two months or less, although new drugs with activity against MDR- and XDR-TB and latent TB are also needed.

In the past, we have synthesized several 1,5-diarylpyrrole derivatives with very good activity against MTB and non-tuberculosis mycobacteria, also showing low cytotoxicity.[11–17] Structure–activity relationship (SAR) studies and a pharmacophore-based ligand design approach allowed us to identify chemical groups and their substitution pattern on the pyrrole responsible for the activity. In particular, a fluoride or a small alkyl group at the *para*-position of the phenyl rings at N1 and C5 of the pyrrole and the thiomorpholinomethyl at C3 were found as the most profitable assembly for antimycobacterial activity.[12–16] As an example, compound **1** (named **BM521**; Chart 1) bearing this arrangement of substituents showed a very low MIC value and a protection index of 272.16 (Table 1). On this basis, we report herein the design, synthesis and evaluation of new pyrrole derivatives (compounds **2**–**29**) obtained by isosteric and bioisosteric replacement of groups at the phenyl rings, keeping fixed the substituent at the C3 position of the pyrrole core.

Abbreviations: TB, tuberculosis; MTB, *Mycobacterium tuberculosis*; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug resistant tuberculosis; SAR, Structure–activity relationships; MIC, minimum inhibitory concentration; CC_{50}, 50% cytotoxic concentration; OADC, oleic acid albumin and dextrose complex; PI, protection index; INH-R, isoniazid-resistant; RMP-R, rifampin-resistant; FCS, foetal calf serum.

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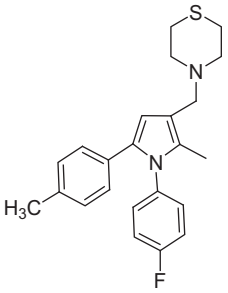
doi:10.1016/j.bmc.2010.09.006



compound **1 (BM521)**

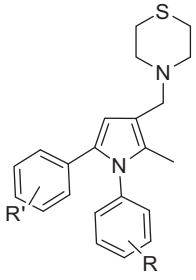
Chart 1. Chemical structure of compound **1** (**BM521**).

2. Material and methods

2.1. Chemistry

A Discovery Microwave System apparatus (from CEM) was used for the Stetter and Paal-Knorr reactions. All chemicals used possess a purity of >95%. Yields refer to purified products and are not optimized. Melting points were determined in open capillaries on a Gallenkamp apparatus and are uncorrected. Microanalyses were conducted on a Perkin-Elmer 240C or a Perkin-Elmer Series II CHNS/O Analyzer 2400 instrument. Fluka Silica Gel 60 (230–400 mesh) was used for column chromatography. Fluka TLC plates (Silica Gel 60 F254) were used for thin-layer chromatography (TLC). Fluka aluminium oxide (activity II–III, according to Brockmann)

Table 1
Structure, in vitro antimycobacterial activity against *M. tuberculosis* H37Rv and *M. tuberculosis* CIP 103471, cytotoxicity (CC_{50}), and protection index (PI) of the new pyrrole derivatives **2**–**29** and reference compounds



1-29

Compound	R	R′	MIC (μg/mL) *M. tuberculosis* H37rv	MIC (μg/mL) *M. tuberculosis* 103471	CC_{50} (μg/mL)	PI[a]
1 (BM521)	4-F	4-CH_3	0.125	0.25	68.04	272.16
2	4-F	2-CF_3	ND	>16	5.21	—
3	2-CF_3	4-F	ND	4	2.58	0.65
4	4-F	4-CF_3	ND	1	8.46	8.46
5	4-CF_3	4-F	ND	8	2.37	0.29
6	4-F	2-OCH_3	ND	>16	10.82	—
7	2-OCH_3	4-F	ND	>16	10.40	—
8	4-F	4-OCH_3	ND	0.25	>120	>480
9	4-OCH_3	4-F	ND	4	21.30	5.32
10	4-F	2-SCH_3	16	16	22.27	1.39
11	2-SCH_3	4-F	8	8	33.99	4.20
12	4-F	4-SCH_3	<0.125	0.125	>128	>1000
13	4-SCH_3	4-F	1	1	>128	>128
14	4-OCH_3	4-CH_3	1	2	13.13	6.57
15	4-CH_3	4-OCH_3	0.50	0.25	11.55	46.20
16	4-OCH_3	4-C_2H_5	0.50	0.50	18.03	36.06
17	4-C_2H_5	4-OCH_3	0.50	0.25	15.76	63.04
18	4-OCH_3	4-C_3H_7	0.50	0.25	>128	>512
19	4-C_3H_7	4-OCH_3	0.25	0.25	12.28	49.12
20	4-OCH_3	4-*i*-C_3H_7	0.50	0.50	4.88	9.76
21	4-*i*-C_3H_7	4-OCH_3	0.25	0.25	10.22	40.88
22	4-SCH_3	4-CH_3	1	1	69.06	69.06
23	4-CH_3	4-SCH_3	0.25	0.25	18.40	73.60
24	4-SCH_3	4-C_2H_5	1	0.25	25.74	102.96
25	4-C_2H_5	4-SCH_3	0.25	0.25	17.18	68.72
26	4-SCH_3	4-C_3H_7	0.50	0.25	89.92	359.68
27	4-C_3H_7	4-SCH_3	0.50	0.125	25.25	202.00
28	4-SCH_3	4-*i*-C_3H_7	0.50	0.50	114.95	229.90
29	4-*i*-C_3H_7	4-SCH_3	0.50	0.125	37.58	286.24
S[b]			0.50	0.50	>1000	>2000
R[c]			0.25	0.25	207.03	828.12

ND: not determined.
[a] PI: protection index, expressed as CC_{50}/MIC ratio.
[b] S: streptomycin.
[c] R: rifampin.

was used for chromatographic purifications. Fluka Stratocrom aluminium oxide plates with a fluorescent indicator were used for TLC to check the purity of the compounds. HPLC Analysis was conducted using a Waters Alliance 2695 instrument, using a UV–vis Waters PDA 996 detector and working at 333 nm. Millennium Empower with Windows XP was used. A Phenomenex LUNA C8, 5 μm (150 × 4.6 mm) column (code 00F-4249-E0), at 40 °C, was used as the chromatographic column at a flow rate of 1.0 mL/min. All the synthesized compounds were ⩾95% pure. ^{13}C NMR and ^{1}H NMR spectra were recorded with a Bruker AC 400 spectrometer in the indicated solvent (TMS as the internal standard). The values of the chemical shifts are expressed in parts per million.

Compounds **2**–**29** were prepared as shown in Scheme 1. Briefly, 1,4-diketones **32a**–**k** were obtained by reacting the suitable benzaldehyde **30a**–**k** with methyl vinyl ketone **31** in the Discovery Microwave System apparatus. Compounds **32a**–**k** cyclized, in the presence of the appropriate amine, to yield the expected 1,5-diarylpyrroles **33a**–**b′**. Finally, reacting compounds **33a**–**b′** with formaldehyde and thiomorpholine, following Mannich reaction conditions, final compounds **2**–**29** were obtained.

2.2. Microbiology

Antimycobacterial activity and cytotoxic activity assays were performed following a protocol previously reported.[14,16] Compounds **2**–**9** were preliminarily assayed against to freshly isolated clinical strains, *M. furtuitum* CA10 and *M. tuberculosis* B814, according to the dilution method in agar. Growth media were Mueller-Hilton (Difco) containing 10% of OADC (oleic acid, albumin and dextrose complex) for *M. furtuitum* and Middlebrook 7H11 agar (Difco) with 10% of OADC for *M. tuberculosis*. Substances were tested at single dose of 100 μg/mL. The active compounds were then assayed for inhibitory activity against a panel of mycobacteria (*M. tuberculosis* CIP 103471, *M. tuberculosis* H37Rv ATCC 27294, isoniazid-resistant *M. tuberculosis* ATCC and rifampin-resistant *M. tuberculosis* ATCC) in Middlebrook 7H11 agar by a standard two-fold dilution method. Plates were incubated at 37 °C for 3 or 28 days. **BM521**, rifampin and streptomycin were used as reference compounds. After cultivation, MICs were read as minimal concentrations of drugs completely inhibiting visible growth of mycobacteria.

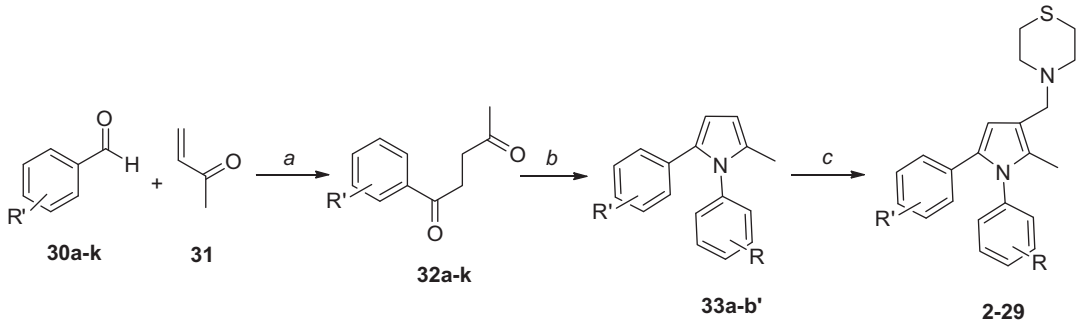
The murine macrophage-like cell line J774.A1 was maintained in Dulbecco's modified Eagle's medium supplemented with 10% foetal calf serum (FCS). Cells were plated at density of 0.5 × 10^6 cells per well in 24-well plates and overlaid with a *M. tuberculosis* suspension adjusted to yield a multiplicity of infection of 20 bacteria per macrophage. Cells were then treated with the tested compound and lysed after 3 and 7 days of incubation by addiction of 0.25% of sodium lauryl sulphate in PBS. Lysates were neutralized by the addition of 15% bovine serum albumin in saline and aliquots of 10-fold dilutions were plated onto 7H10 agar. CFU of *M. tuberculosis* were counted after 28 days incubation at 37 °C.

The cytotoxicity was evaluated on Vero cells grown and maintained in RPMI 1640 medium supplemented with 2 mM L-glutamine and 10% FCS. Cells were seeded in 96-well plates at a density of 1 × 10^4 cells/well. After 24 h, medium was replaced with fresh medium containing decreasing concentrations of the tested compound and incubated at 37 °C in 5% CO_2. Cells were observed for morphological changes at 24, 48 and 72 h of incubation. After 72 h the effects on the proliferation of Vero cells were determined by tetrazolium-based colorimetric MTT assay. The 50% cell-inhibitory concentration (CC_{50}) reduced by 50% the optical density values ($OD_{540,690}$) with respect to control no-drug treated cells.

Protection index (PI) is CC_{50}/MIC ratio (considering *M. tuberculosis* 103471).

3. Results and discussion

Initially, on the basis of previous results we synthesized new analogs of **1**, in which the methyl group on the phenyl ring was replaced with the isosteric trifluoromethyl one placed at *para*- and *ortho*-positions (compounds **2**–**5**). However, they did not show a good antimycobacterial activity. In fact, only **4** proved to be active against *M. tuberculosis* (MIC 1 μg/mL) even if it is slightly cytotoxic (CC_{50} 8 μg/mL, Table 1). Next, to further explore the substitution requirements of the phenyl ring, the trifluoromethyl substituent was replaced with a methoxyl one (compounds **6**–**9**). Only **8** proved to be active against *M. tuberculosis* (MIC 0.25 μg/mL) and to have low cytotoxicity (CC_{50} higher than 120). By using **8** as template, **10**–**13** were designed and synthesized by replacing the methoxyl substituent with the bioisosteric methylsulfanyl group. Notably, **12** (named **BM579**), bearing a N1 *p*-F phenyl group already found as the optimal substituent for enhancing the antimycobacterial activity of 1,5-diarylpyrrole derivatives,[22] showed an activity against *M. tuberculosis* 103471 (<0.125 μg/mL) better than those shown by the currently available antitubercular drugs streptomycin and rifampin, as well as better than that of previous parent compounds **1** and **8**. Although the antimycobacterial activity of **12** was slightly ameliorated with respect to that found for previous



Scheme 1. Synthetic pathway of compounds **2**–**29**. Compounds: **30a**: R' = 4-F; **30b**: R' = 2-CF_3; **30c**: R' = 4-CF_3; **30d**: R' = 2-OCH_3; **30e**: R' = 4-OCH_3; **30f**: R' = 2-SCH_3; **30g**: R' = 4-SCH_3; **30h**: R' = 4-CH_3; **30i**: R' = 4-C_2H_5; **30j**: R' = 4-C_3H_7; **30k**: R' = 4-iC_3H_7; **32a**: R' = 4-F; **32b**: R' = 2-CF_3; **32c**: R' = 4-CF_3; **32d**: R' = 2-OCH_3; **32e**: R' = 4-OCH_3; **32f**: R' = 2-SCH_3; **32g**: R' = 4-SCH_3; **32h**: R' = 4-CH_3; **32i**: R' = 4-C_2H_5; **32j**: R' = 4-C_3H_7; **32k**: R' = 4-iC_3H_7; **33a**: R = 4-F; R' = 2-CF_3; **33b**: R = 2-CF_3; R' = 4-F; **33c**: R = 4-F; R' = 4-CF_3; **33d**: R = 4-CF_3; R = 4-F; **33e**: R = 4-F; R' = 2-OCH_3; **33f**: R = 2-OCH_3; R' = 4-F; **33g**: R = 4-F; R' = 4-OCH_3; **33h**: R = 4-OCH_3; R' = 4-F; **33i**: R = 4-F; R' = 2-SCH_3; **33j**: R = 2-SCH_3; R=4-F; **33k**: R = 4-F; R' = 4-SCH_3; 331: R = 4-SCH_3; R = 4-F; **33m**: R = 4-OCH_3; R' = 4-CH_3; **33n**: R = 4-CH_3; R' = 4-OCH_3; **33o**: R = 4-OCH_3; R' = 4-C_2H_5; **33p**: R = 4-C_2H_5; R' = 4-OCH_3; **33q**: R = 4-OCH_3; R' = 4-C_3H_7; **33r**: R = 4-C_3H_7; R' = 4-OCH_3; **33s**: R = 4-OCH_3; R' = 4-iC_3H_7; **33t**: R = 4-iC_3H_7; R' = 4-OCH_3; **33u**: R = 4-SCH_3; R' = 4-CH_3; **33v**: R = 4-CH_3; R' = 4-SCH_3; **33w**: R = 4-SCH_3; R' = 4-C_2H_5; **33x**: R = 4-C_2H_5; R' = 4-SCH_3; **33y**: R = 4-SCH_3; R' = 4-C_3H_7; **33z**: R = 4-C_3H_7; R' = 4-SCH_3; **33a′**: R = 4-SCH_3; R' = 4-iC_3H_7; **33b′**: R = 4-iC_3H_7; R' = 4-SCH_3. Reagents and conditions: (a) 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide, TEA, mw, 15 min; (b) $H_2NC_6H_4R$, *p*-toluensulfonic acid, EtOH, mw 30 min; (c) (1) thiomorpholine, CH_3CN, HCHO, CH_3COOH, rt, 3 h; (2) NaOH 20% w/v.

parent pyrrole analogues, the ability of **12** to inhibit *M. tuberculosis* H37Rv was even better than that of all the reference compounds. In addition, it was characterized by a very good protection index (PI), which is significantly higher than that found for rifampin. This is particularly important considering that antimycobacterial drugs are very often administered to immune-compromised patients for which drug toxicity is the effective cause of death. Compound **12** was also tested against resistant *M. tuberculosis* strains [namely, isoniazid-resistant (INH-R) and rifampin-resistant (RMP-R)] and showed a very good antimycobacterial activity against the RMP-R strain (0.25 μg/mL), while it was inactive (>16 μg/mL) against the INH-R strain (Table 2). Current drugs are poorly active or inactive against drug-resistant mycobacteria; therefore, a multi-drug therapy is needed. In this context, it is suggested that **12** may be used alone or in combination with other antitubercular compounds for the treatment of tuberculosis. Furthermore, it is noteworthy that **12** exerted a bactericidal activity on intracellular *M. tuberculosis*, determined at several concentrations using the J774.A1 murine macrophage cell line infected with *M. tuberculosis* H37Rv.[18] At the concentration of 0.125 μg/mL, a 96.12% reduction of the tubercular bacilli survival was observed with compound **12**, comparable to the reduction induced by rifampin (Table 3).

Finally, to extend our SAR studies, we decided to combine the best substituents responsible for the good activity of compounds **2**–**13** with longer alkyl chain, on the basis of the good results previously obtained with a further increase of lipophilicity of the compounds.[16] Therefore, compounds **14**–**29**, in which a *p*-methoxyl (as for **8** and **9**), a *p*-methylsulfanyl (as for **12** and **13**) or a *p*-alkyl (ethyl, propyl, and isopropyl) group is placed on the phenyl ring at N1 or C5, were designed and synthesized. In principle, compounds **14**–**29** showed a very good biological profile (Table 1). In fact, all of them showed MIC values ranging from 0.125 to 2 μg/mL, while only few compounds also had a low cytotoxicity, thus leading to high values of the protection index. As examples, **18**, **22**, **26**, **28**, and **29** are characterized by CC_{50} values from 37.58 to 128 μg/mL thus resulting in PI values ranging from 69.06 to >512.

4. Conclusion

To summarize, the most active and safe compound of each of the three subseries obtained by replacing the methyl group at the *para*-position of the C5 phenyl ring of compound **1** with a CF_3 (**2**–**5**), a methoxy (**6**–**9**) and a methylsulphanyl (**10**–**13**) substituent, was characterized by the same substitution pattern as compound **1**. In fact, compounds **4**, **8**, and **12** had a *p*-F phenyl ring at N1 and a thiomorpholinomethyl moiety at C3. Moreover, these results further confirm that the *p*-F phenyl ring at N1 is one of the most profitable moieties for antimycobacterial activity. The hypothesis that the preferential substitution pattern on the pyrrole ring is that found for compound **1** is also confirmed by the activity found for compounds **14**–**29**. In fact, compounds with the alkyl substituent at the N1 phenyl ring are in general more active than the corresponding analogues bearing the same group at C5. Some of the new derivatives showed an in vitro activity against *M. tuberculosis* better than that found for previous parent pyrrole derivatives, as well as better than that of the antitubercular drugs streptomycin and rifampin. In addition, several of them proved to be less cytotoxic than rifampin. Among the compounds reported herein, compound **12** is arguably the most potent and our present study makes it an interesting compound when compared to the current therapies.

Table 2
In vitro antimycobacterial activity (against INH-R and RMP-R *M. tuberculosis* strains) of compound **12** and reference compounds

Compound	MIC (μg/mL) *M. tuberculosis* INH-R	MIC (μg/mL) *M. tuberculosis* RMP-R
1 (BM521)	32	0.50
12	>16	0.25
S[a]	0.50	0.50
R[b]	0.80	>64

[a] S: Streptomycin.
[b] R: Rifampin.

Table 3
Intracellular antimycobacterial activity of compounds **12** and Rifampicin against intracellular *M. tuberculosis*

Compound	1 μg/mL	0.5 μg/mL	0.25 μg/mL	0.125 μg/mL
12	99.81	99.72	99.02	96.12
R[a]	99.97	99.93	99.83	96.59

Data are expressed as % of growth reduction respect to untreated controls after 6 days of treatment.
[a] R: Rifampin.

5. Experimental details

5.1. General procedure for the preparation of pentane-1,4-diones 32a–k

Following the Stetter reaction, a mixture of the appropriate benzaldehyde **30a**–**k** (0.09 mol), triethylamine (19.5 mL, 0.14 mol), methyl vinyl ketone **31** (0.09 mol), and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (3.53 g, 0.014 mol) (Scheme 1) was put into a round-bottom flask equipped with a stir bar. The flask was inserted into the cavity of a Discovery Microwave System apparatus and heated (150 W for 15 min, internal temperature 70 °C, and internal pressure 60 psi). The residue was treated with 10 ml of 2 N HCl. After extraction with ethyl acetate, the organic layer was washed with aqueous sodium bicarbonate and water. The organic fractions were dried over Na_2SO_4, filtered, and concentrated to give a crude orange liquid. After chromatography on aluminum oxide (activity II–III, according to Brockmann) (cyclohexane/ethyl acetate, 3:1 v/v), the desired **32a**–**k** were isolated as a light-yellow solids which, after recrystallization from cyclohexane, gave an analytical sample as needles.

5.1.1. 1-[4-(Fluoro)phenyl]-pentane-1,4-dione (32a)
Yellowish needles (yield 75%). Analytical data, mp, and ^{1}H NMR spectrum were consistent with literature.[18]

5.1.2. 1-[2-(Trifluoromethyl)phenyl]-pentane-1,4-dione (32b)
Yellowish needles (yield 80%), mp 75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06–7.04 (m, 1H), 7.00–7.02 (m, 3H), 3.49 (t, J = 6.7 Hz, 2H), 2.71 (t, J = 6.7 Hz, 2H), 2.12 (s, 3H). Anal. ($C_{12}H_{11}O_2F_3$) C, H, F.

5.1.3. 1-[4-(Trifluoromethyl)phenyl]-pentane-1,4-dione (32c)
Yellowish needles (yield 75%). Analytical data, mp, and ^{1}H NMR spectrum were consistent with literature.[19]

5.1.4. 1-[2-(Methoxy)phenyl]-pentane-1,4-dione (32d)
Yellowish needles (yield 66%). Analytical data, mp, and ^{1}H NMR spectrum were consistent with literature.[20]

5.1.5. 1-[4-(Methoxy)phenyl]-pentane-1,4-dione (32e)
Yellowish needles (yield 70%). Analytical data, mp, and ^{1}H NMR spectrum were consistent with literature.[21]

5.1.6. 1-[2-(Methylthio)phenyl]-pentane-1,4-dione (32f)
Yellowish needles (yield 65%), mp 60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12–7.13 (m, 1H), 7.06–7.08 (m, 3H), 3.50 (t, J = 6.7 Hz,

2H), 2.75 (t, J = 6.7 Hz, 2H), 2.29 (s, 3H), 2.13 (s, 3H). Anal. ($C_{13}H_{14}O_2S$) C, H, S.

5.1.7. 1-[4-(Methylthio)phenyl]-pentane-1,4-dione (32g)

Yellowish needles (yield 80%). Analytical data, mp, and ^{1}H NMR spectrum were consistent with literature.[22]

5.1.8. 1-[4-(Methyl)phenyl]-pentane-1,4-dione (32h)

White needles (yield 76%). Analytical data, mp, and ^{1}H NMR spectrum were consistent with literature.[23]

5.1.9. 1-[4-(Ethyl)phenyl]-pentane-1,4-dione (32i)

Yellow oil (yield 60%). Analytical data, mp, and ^{1}H NMR spectrum were consistent with literature.[16]

5.1.10. 1-[4-(Propyl)phenyl]-pentane-1,4-dione (32j)

Yellow oil (yield 63%). Analytical data, mp, and ^{1}H NMR spectrum were consistent with literature.[16]

5.1.11. 1-[4-(*i*-Propyl)phenyl]-pentane-1,4-dione (32k)

Yellow oil (yield 68%). Analytical data, mp, and ^{1}H NMR spectrum were consistent with literature.[16]

5.2. General procedure for the preparation of 1,5-diarylpyrroles 33a–b′

Following the Paal-Knorr reaction, the proper diketone **32** (2.28 mmol) was dissolved in ethanol (2 mL) into a round-bottom flask equipped with a stir bar. The suitable amine (2.28 mmol) and *p*-toluenesulfonic acid (30 mg, 0.17 mmol) were added. The flask was inserted into the cavity of the Discovery Microwave System apparatus and heated (150 W for 30 min, internal temperature 160 °C, and internal pressure 150 psi). The reaction mixture was cooled and concentrated. The crude material was purified by chromatography on aluminum oxide (activity II–III, according to Brockmann) with cyclohexane as the eluant to give the expected 1,5-diarylpyrroles **33a**–**b′** as solids in satisfactory yield.

5.2.1. 2-Methyl-5-[2-(trifluoromethyl)phenyl]-1-[4-(fluoro) phenyl]-1*H*-pyrrole (33a)

White needles (yield 50%), mp 185 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.60 (m, 1H), 7.32–7.29 (m, 2H), 7.11–7.09 (m, 5H), 6.34 (d, J = 3.5 Hz, 1H), 6.11 (d, J = 3.5 Hz, 1H), 2.07 (s, 3H). Anal. ($C_{18}H_{13}F_4N$) C, H, N, F.

5.2.2. 2-Methyl–5-[4-(fluoro)phenyl]-1-[2-(trifluoromethyl) phenyl]-1*H*-pyrrole (33b)

White needles (yield 70%), mp 197 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.69 (m, 2H), 7.53–7.52 (m, 1H), 7.41–7.37 (m, 1H), 7.00–6.98 (m, 2H), 6.83–6.79 (m, 2H), 6.35 (d, J = 3.5 Hz, 1H), 6.13 (d, J = 3.5 Hz, 1H), 1.91 (s, 3H). Anal. ($C_{18}H_{13}F_4N$) C, H, N, F.

5.2.3. 2-Methyl-5-[4-(trifluoromethyl)phenyl]-1-[4-(fluoro) phenyl]-1*H*-pyrrole (33c)

White needles (yield 65%), mp 101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 7.27 Hz, 2H), 7.24 (d, J = 7.27 Hz, 2H), 7.13–7.10 (m, 4H), 6.37 (d, J = 3.5 Hz, 1H), 6.10 (d, J = 3.5 Hz, 1H), 2.10 (s, 3H). Anal. ($C_{18}H_{13}F_4N$) C, H, N, F.

5.2.4. 2-Methyl-5-[4-(fluoro)phenyl]-1-[4-(trifluoromethyl) phenyl]-1*H*-pyrrole (33d)

White needles (yield 63%), mp 198 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.27 Hz, 2H), 7.38 (d, J = 7.27 Hz, 2H), 7.05 (d, J = 7.27 Hz, 2H), 7.02 (d, J = 7.27 Hz, 2H), 6.33 (d, J = 3.5 Hz, 1H), 6.11 (d, J = 3.5 Hz, 1H), 2.09 (s, 3H). Anal. ($C_{18}H_{13}F_4N$) C, H, N, F.

5.2.5. 2-Methyl-5-[2-(methoxy)phenyl]-1-[4-(fluoro)phenyl]-1*H*-pyrrole (33e)

White needles (yield 50%), mp 186 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.22 (m, 7H), 6.68–6.63 (m, 1H), 6.30 (m, J = 3.5 Hz, 1H), 6.09 (d, J = 3.5 Hz, 1H), 2.07 (s, 3H). Anal. ($C_{18}H_{16}FNO$) C, H, N, F.

5.2.6. 2-Methyl-5-[4-(fluoro)phenyl]-1-[2-(methoxy)phenyl]-1*H*-pyrrole (33f)

White needles (yield 52%), mp 195 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.09 (m, 2H), 7.04–7.00 (m, 4H), 6.86–6.82 (m, 2H), 6.30 (d, J = 3.5 Hz, 1H), 6.11 (d, J = 3.5 Hz, 1H), 2.06 (s, 3H). Anal. ($C_{18}H_{16}FNO$) C, H, N, F.

5.2.7. 2-Methyl-5-[4-(methoxy)phenyl]-1-[4-(fluoro)phenyl]-1*H*-pyrrole (33g)

Yellowish needles (yield 78%), mp 85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.09 (m, 4H), 7.08 (d, J = 7.27 Hz, 2H), 6.96 (d, J = 7.27 Hz, 2H), 6.29 (d, J = 3.5 Hz, 1H), 6.14 (d, J = 3.5 Hz, 1H), 3.81 (s, 3H), 2.07 (s, 3H). Anal. ($C_{18}H_{16}FNO$) C, H, N, F.

5.2.8. 2-Methyl-5-[4-(fluoro)phenyl]-1-[4-(methoxy)phenyl]-1*H*-pyrrole (33h)

White needles (yield 70%), mp 185 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08–7.00 (m,4H), 6.90–6.84 (m, 4H), 6.26 (d, J = 3.5 Hz, 1H), 6.10 (d, J = 3.5 Hz, 1H), 3.77 (s, 3H), 2.03 (s, 3H). Anal. ($C_{18}H_{16}FNO$) C, H, N, F, O.

5.2.9. 2-Methyl-5-[2-(methylthio)phenyl]-1-[4-(fluoro)phenyl]-1*H*-pyrrole (33i)

White needles (yield 57%), mp 112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.08 (m, 1H), 7.07–7.03 (m, 3H), 6.97–6.90 (m, 4H), 6.29 (d, J = 3.5 Hz, 1H), 6.13 (d, J = 3.5 Hz, 1H), 2.55 (s, 3H), 2.08 (s, 3H). Anal. ($C_{18}H_{16}FNS$) C, H, N, F, S.

5.2.10. 2-Methyl-5-[4-(fluoro)phenyl]-1-[2-(methylthio)phenyl]-1*H*-pyrrole (33j)

White needles (yield 91%), mp 96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.22 (m, 1H), 7.15–7.09 (m, 5H), 6.82–6.74 (m, 2H), 6.31 (d, J = 3.5 Hz, 1H), 6.11 (d, J = 3.5 Hz, 1H), 2.53 (s, 3H), 1.99 (s, 3H). Anal. ($C_{18}H_{16}FNS$) C, H, N, F, S.

5.2.11. 2-Methyl-5-[4-(methylthio)phenyl]-1-[4-(fluoro)phenyl]-1*H*-pyrrole (33k)

White needles (yield 93%). Analytical data, mp, and ^{1}H NMR spectrum were consistent with literature.[22]

5.2.12. 2-Methyl-5-[4-(fluoro)phenyl]-1-[4-(methylthio)phenyl]-1*H*-pyrrole (33l)

White needles (yield 92%), mp 114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.30 (m, 2H), 7.15–7.09 (m, 4H), 7.07–7.00 (m, 2H), 6.35 (d, J = 3.5 Hz, 1H), 6.08 (d, J = 3.5 Hz, 1H), 2.60 (s, 3H), 2.06 (s, 3H). Anal. ($C_{18}H_{16}FNS$) C, H, N, F, S.

5.2.13. 2-Methyl-5-[4-(methyl)phenyl]-1-[4-(methoxy)phenyl]-1*H*-pyrrole (33m)

White needles (yield 66%), mp 137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 7.27 Hz, 2 H), 6.94 (m, 4H), 6.88 (d, J = 7.27 Hz, 2H), 6.28 (d, J = 3.5 Hz, 1H), 6.09 (d, J = 3.5 Hz, 1H), 3.81 (s, 3H), 2.40 (s, 3H), 2.05 (s, 3H). Anal. ($C_{19}H_{19}NO$) C, H, N.

5.2.14. 2-Methyl-5-[4-(methoxy)phenyl]-1-[4-(methyl)phenyl]-1*H*-pyrrole (33n)

White needles (yield 66%), mp 85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22(d, J = 7.27 Hz, 2H), 7.03 (d, J = 7.27 Hz, 2H), 6.98–6.90 (m, 4H), 6.29 (d, J = 3.5 Hz, 1H), 6.11 (d, J = 3.5 Hz, 1H), 3.81 (s, 3H), 2.40 (s, 3H), 2.05 (s, 3H). Anal. ($C_{19}H_{19}NO$) C, H, N.

5.2.15. 2-Methyl-5-[4-(ethyl)phenyl]-1-[4-(methoxy)phenyl]-1*H*-pyrrole (33o)

White needles (yield 80%), mp 71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 7.27 Hz, 2 H), 6.95 (s, 4H), 6.84 (d, J = 7.27 Hz, 2H), 6.31 (d, J = 3.5 Hz, 1H), 6.11 (d, J = 3.5 Hz, 1H), 3.78 (s, 3H), 2.77 (q, J = 7.1 Hz, 2H), 2.04 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H). Anal. ($C_{20}H_{21}NO$) C, H, N.

5.2.16. 2-Methyl-5-[4-(methoxy)phenyl]-1-[4-(ethyl)phenyl]-1*H*-pyrrole (33p)

Yellowish needles (yield 53%), mp 80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 7.27 Hz, 2 H), 7.02 (d, J = 7.27 Hz, 2H), 6.97 (d, J = 7.27 Hz, 2H), 6.67 (d, J = 7.27 Hz, 2H), 6.24 (d, J = 3.5 Hz, 1H), 6.11 (d, J = 3.5 Hz, 1H), 3.73 (s, 3H), 2.72 (q, J = 7.1 Hz, 2H), 2.05 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H). Anal. ($C_{20}H_{21}NO$) C, H, N.

5.2.17. 2-Methyl-5-[4-(propyl)phenyl]-1-[4-(methoxy)phenyl]-1*H*-pyrrole (33q)

White needles (yield 55%), mp 55 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 7.27 Hz, 2 H), 6.95 (m, 6H), 6.29 (d, J = 3.5 Hz, 1H), 6.09 (s, J = 3.5 Hz, 1H), 3.81 (s, 3H), 2.43 (t, J = 7.1 Hz, 2H), 2.04 (s, 3H), 1.64–1.60 (m, 2H), 0.91 (t, J = 7.1 Hz, 3H). Anal. ($C_{21}H_{23}NO$) C, H, N.

5.2.18. 2-Methyl-5-[4-(methoxy)phenyl]-1-[4-(propyl)phenyl]-1*H*-pyrrole (33r)

Yellowish needles (yield 79%), mp 85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 7.27 Hz, 2H), 7.05 (d, J = 7.27 Hz, 2H), 6.92 (s, 4H), 6.29 (d, J = 3.5 Hz, 1H), 6.09 (d, J = 3.5 Hz, 1H), 3.81 (s, 3H), 2.60 (t, J = 7.1 Hz, 2H), 2.05 (s, 3H), 1.68–1.63 (m, 2H), 0.94 (t, J = 7.1 Hz, 3H). Anal. ($C_{21}H_{23}NO$) C, H, N.

5.2.19. 2-Methyl-5-[4-(*i*-propyl)phenyl]-1-[4-(methoxy)phenyl]-1*H*-pyrrole (33s)

White needles (yield 65%), mp 83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 7.27 Hz, 2H), 6.98 (s, 4H), 6.87 (d, J = 7.27 Hz, 2H), 6.29 (d, J = 3.5 Hz, 1H), 6.11 (d, J = 3.5 Hz, 1H), 3.83 (s, 3H), 2.88–2.84 (m, 1H), 2.03 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H). Anal. ($C_{21}H_{23}NO$) C, H, N.

5.2.20. 2-Methyl-5-[4-(methoxy)phenyl]-1-[4-(*i*-propyl)phenyl]-1*H*-pyrrole (33t)

White needles (yield 66%), mp 84 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 7.27 Hz, 2H), 7.06 (d, J = 7.27 Hz, 2H), 6.98–6.93 (m, 4H), 6.30 (d, J = 3.5 Hz, 1H), 6.09 (d, J = 3.5 Hz, 1H), 3.85 (s, 3H), 2.92–2.88 (m, 1H), 2.06 (s, 3H), 1.27 (s, 3H), 1.20 (s, 3H). Anal. ($C_{21}H_{23}NO$) C, H, N.

5.2.21. 2-Methyl-5-[4-(methyl)phenyl]-1-[4-(methylthio)phenyl]-1*H*-pyrrole (33u)

White needles (yield 73%), mp 91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 7.27 Hz, 2H), 7.13 (d, J = 7.27 Hz, 2H), 6.94 (s, 4H), 6.31 (d, J = 3.5 Hz, 1H), 6.07 (d, J = 3.5 Hz, 1H), 2.49 (s, 3H), 2.25 (s, 3H), 2.06 (s, 3H). Anal. ($C_{19}H_{19}NS$) C, H, N, S.

5.2.22. 2-Methyl-5-[4-(methylthio)phenyl]-1-[4-(methyl)phenyl]-1*H*-pyrrole (33v)

White needles (yield 68%), mp 109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 7.27 Hz, 2H), 7.08–7.00 (m, 6H), 6.31 (d, J = 3.5 Hz, 1H), 6.11 (d, J = 3.5 Hz, 1H), 2.41 (s, 3H), 2.38 (s, 3H), 2.04 (s, 3H). Anal. ($C_{19}H_{19}NS$) C, H, N, S.

5.2.23. 2-Methyl-5-[4-(ethyl)phenyl]-1-[4-(methylthio)phenyl]-1*H*-pyrrole (33w)

White needles (yield 58%), mp 96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 7.27 Hz, 2H), 7.05 (d, J = 7.27 Hz, 2H), 6.98–6.93 (m, 4H), 6.29 (d, J = 3.5 Hz, 1H), 6.07 (d, J = 3.5 Hz, 1H), 2.55 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 2.05 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H). Anal. ($C_{20}H_{21}NS$) C, H, N, S.

5.2.24. 2-Methyl-5-[4-(methylthio)phenyl]-1-[4-(ethyl)phenyl]-1*H*-pyrrole (33x)

Yellowish needles (yield 41%), mp 78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 7.27 Hz, 2H), 7.08–7.00 (m, 6H), 6.28 (d, J = 3.5 Hz, 1H), 6.09 (d, J = 3.5 Hz, 1H), 2.71 (q, J = 7.1 Hz, 2H), 2.42 (s, 3H), 2.05 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H). Anal. ($C_{20}H_{21}NS$) C, H, N, S.

5.2.25. 2-Methyl-5-[4-(propyl)phenyl]-1-[4-(methylthio)phenyl]-1*H*-pyrrole (33y)

White needles (yield 54%), mp 77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 7.27 Hz, 2H), 7.03 (d, J = 7.27 Hz, 2H), 6.98–6.92 (m, 4H), 6.29 (d, J = 3.5 Hz, 1H), 6.07 (d, J = 3.5 Hz, 1H), 2.54–2.48 (m, 5H), 2.05 (s, 3H), 1.60–1.54 (m, 2H), 0.91 (t, J = 7.1 Hz, 3H). Anal. ($C_{21}H_{23}NS$) C, H, N, S.

5.2.26. 2-Methyl-5-[4-(methylthio)phenyl]-1-[4-(propyl)phenyl]-1*H*-pyrrole (33z)

Yellowish needles (yield 75%), mp 87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 7.27 Hz, 2H), 7.08–7.00 (m, 6H), 6.30 (d, J = 3.5 Hz, 1H), 6.10 (d, J = 3.5 Hz, 1H), 2.61 (t, J = 7.1 Hz, 2H), 2.40 (s, 3H), 2.05 (s, 3H), 1.65 (m, J = 7.1 Hz, 2H), 0.93 (s, 3H). Anal. ($C_{21}H_{23}NS$) C, H, N, S.

5.2.27. 2-Methyl-5-[4-(*i*-propyl)phenyl]-1-[4-(methylthio)phenyl]-1*H*-pyrrole (33a′)

White needles (yield 51%), mp 91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 7.27 Hz, 2H), 7.03 (d, J = 7.27 Hz, 2H), 6.94–6.90 (m, 4H), 6.29 (d, J = 3.5 Hz, 1H), 6.09 (d, J = 3.5 Hz, 1H), 2.94–2.90 (m, 1H), 2.38 (s, 3H), 2.06 (s, 3H), 1.27 (s, 3H), 1.20 (s, 3H). Anal. ($C_{21}H_{23}NS$) C, H, N, S.

5.2.28. 2-Methyl-5-[4-(methylthio)phenyl]-1-[4-(*i*-propyl)phenyl]-1*H*-pyrrole (33b′)

White needles (yield 68%), mp 82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 7.27 Hz, 2H), 7.08–7.03 (m, 6H), 6.30 (d, J = 3.5 Hz, 1H), 6.07 (d, J = 3.5 Hz, 1H), 2.83–2.80 (m,1H), 2.41 (s, 3H), 2.06 (s, 3H), 1.28 (s, 3H), 1.25 (s, 3H). Anal. ($C_{21}H_{23}NS$) C, H, N,S.

5.3. General procedure for the preparation of compounds 2–29

Following the Mannich reaction, to a stirred solution of an appropriate pyrrole **33a**–**b**′ (5.6 mmol) in acetonitrile (20 mL), a mixture of thiomorpholine (0.57 g, 5.6 mmol), formaldehyde (0.18 g, 5.6 mmol) (40% in water), and 5 mL of acetic acid was added dropwise. After the addition was complete, the mixture was stirred at room temperature for 1 h and then treated with a solution of sodium hydroxide (20%, w/v) and extracted with ethyl acetate. The organic extracts were combined, washed with water, and dried. After removal of solvent, the residue was purified by column chromatography, using silica gel and petroleum ether/ethyl acetate (3:1 v/v). The eluates were combined after TLC control and the solvent was removed to give **2–29** as solids in satisfactory yield. Recrystallization from diethyl ether gave compounds **2–29** as solids in satisfactory yields.

5.3.1. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[2-(trifluoromethyl)phenyl]-1-[4-(fluoro)phenyl]-1*H*-pyrrole (2)

Yellow oil (yield 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.60 (m, 1H), 7.24 (d, J = 7.27 Hz, 2H), 7.08–7.03 (m, 5H), 6.26 (s, 1H), 3.49 (s, 2H), 2.82–2.77 (m, 4H), 2.73–2.70 (m, 4H), 2.06 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.61, 28.14, 50.01, 55.30, 110.66, 113.95, 115.00, 116.19, 124.14, 127.54, 127.59, 127.64, 127.69,

128.90, 128.97, 129.00, 129.32, 129.40, 129.45, 130.77, 132.35, 132.59, 133.25, 137.55, 159.10, 162.41. Anal. ($C_{23}H_{22}F_4N_2S$) C, H, N, F, S.

5.3.2. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(fluoro) phenyl]-1-[2-(trifluoromethyl)phenyl]-1*H*-pyrrole (3)

White needles (yield 48%), mp 130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.27 Hz, 2H), 7.55–7.48 (m, 1H), 7.33–7.30 (m, 1H), 6.96 (d, J = 7.27 Hz, 2H), 6.73–6.68 (m, J = 7.27 Hz, 2H), 6.30 (s, 1H), 3.52 (s, 2H), 2.76–2.70 (m, 4H), 2.55–2.52 (m, 4H), 2.33 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.61, 28.14, 54.01, 55.30, 110.70, 114.00, 114.98, 116.15, 124.55, 127.54, 127.59, 127.64, 127.69, 128.90, 128.97, 129.00, 129.32, 129.40, 129.45, 130.77, 132.35, 132.59, 133.25, 137.55, 159.10, 162.41. Anal. ($C_{23}H_{22}F_4N_2S$) C, H, N, F, S.

5.3.3. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(trifluoromethyl)phenyl]-1-[4-(fluoro)phenyl]-1*H*-pyrrole (4)

White needles (yield 57%), mp 145 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 7.27 Hz, 2H), 7.26 (d, J = 7.27 Hz, 2H), 7.15–7.10 (m, 4H), 6.49 (s, 1H), 3.52 (s, 2H), 2.86–2.82 (m, 4H), 2.80–2.76 (m, 4H), 2.10 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.59, 28.41, 54.56, 55.44, 110.99, 114.08, 114.90, 116.27, 125.44, 126.30, 126.35, 126.40, 126.45, 128.77, 129.00, 129.21, 130.11, 130.45, 130.80, 132.36, 132.60, 137.51, 158.50, 161.61. Anal. ($C_{23}H_{22}F_4N_2S$) C, H, N, F, S.

5.3.4. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(fluoro) phenyl]-1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole (5)

Yellow oil (yield 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.27 Hz, 2H), 7.41 (d, J = 7.27 Hz, 2H), 7.05 (d, J = 7.27 Hz, 2H), 7.02 (d, J = 7.27 Hz, 2H), 6.30 (s, 1H), 3.38 (s, 2H), 2.68–2.64 (m, 4H), 2.60–2.56 (m, 4H), 2.09 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.45, 28.45, 49.89, 55.66, 111.09, 114.10, 114.98, 116.30, 125.31, 126.25, 126.40, 126.45, 126.50, 128.81, 129.10, 129.32, 130.12, 130.47, 130.56, 132.36, 133.00, 137.51, 158.45, 161.56. Anal. ($C_{23}H_{22}F_4N_2S$) C, H, N, F, S.

5.3.5. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[2-(methoxy)phenyl]-1-[4-(fluoro)phenyl]-1*H*-pyrrole (6)

White needles (yield 39%), mp 123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.23 (m, 7H), 6.68–6.63 (m, 1H), 6.22 (s, 1H), 3.53 (s, 2H), 3.38 (s, 3H), 2.80–2.76 (m, 4H), 2.66–2.60 (m, 4H), 2.07 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.56, 29.00, 49.90, 55.70, 56.20, 113.91, 114.10, 119.00, 119.60, 127.50, 128.11, 128.40, 129.40, 131.11, 131.62, 136.50, 137.67, 138.50, 159.05, 162.00. Anal. ($C_{23}H_{25}FNOS$) C, H, N, F, S.

5.3.6. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(fluoro) phenyl]-1-[2-(methoxy)phenyl]-1*H*-pyrrole (7)

White needles (yield 40%), mp 123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.08 (m, 2H), 7.04–7.00 (m, 4H), 6.82–6.79 (m, 2H), 6.29 (s, 1H), 3.67 (s, 3H), 3.48 (s, 2H), 2.80–2.76 (m, 4H), 2.72–2.68 (m, 4H), 1.98 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.66, 28.10, 49.60, 55.65, 56.33, 114.01, 114.12, 119.03, 119.40, 127.10, 128.11, 128.43, 129.22, 131.01, 131.70, 136.20, 137.67, 138.50, 159.49, 162.50. Anal. ($C_{23}H_{25}FNOS$) C, H, N, F, S.

5.3.7. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(methoxy)phenyl]-1-[4-(fluoro)phenyl]-1*H*-pyrrole (8)

White needles (yield 20%), mp 120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.10 (m, 4H), 7.08 (d, J = 7.27 Hz, 2H), 6.96 (d, J = 7.27 Hz, 2H), 6.26 (s, 1H), 3.76 (s, 3H), 3.50 (s, 2H), 2.82–2.78 (m, 4H), 2.78–2.74 (m, 4H), 2.07 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.37, 29.01, 49.00, 55.68, 56.27, 113.92, 114.03, 119.12, 119.50, 128.10, 128.43, 129.20, 131.15, 131.61, 136.50, 138.51, 159.60, 162.92. Anal. ($C_{23}H_{25}FNOS$) C, H, N, F, S.

5.3.8. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(fluoro) phenyl]-1-[4-(methoxy)phenyl]-1*H*-pyrrole (9)

White needles (yield 52%), mp 130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04–7.00 (m, 4H), 6.88–6.84 (m, 4H), 6.26 (s, 1H), 3.79 (s, 3H), 3.45 (s, 2H), 2.78–2.76 (m, 4H), 2.70–2.68 (m, 4H), 2.03 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 11.07, 29.01, 49.00, 53.68, 56.33, 113.80, 114.80, 120.33, 120.55, 128.10, 128.20, 129.60, 131.10, 131.77, 136.44, 138.62, 158.93, 162.88. Anal. ($C_{23}H_{25}FNOS$) C, H, N, F, S.

5.3.9. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[2-(methylthio)phenyl]-1-[4-(fluoro)phenyl]-1*H*-pyrrole (10)

White needles (yield 75%), mp 156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10–7.06 (m, 1H), 7.087.04 (m, 3H), 6.95–6.92 (m, 4H), 6.26 (s, 1H), 3.52 (s, 2H), 2.82–2.78 (m, 4H), 2.74–2.70 (m, 4H), 2.33 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.30, 22.30, 28.33, 49.30, 55.60, 113.22, 114.32, 119.12, 120.25, 124.46, 128.30, 128.22, 129.51, 131.23, 131.61, 135,13, 136.53, 138.58, 158.22, 161.90. Anal. ($C_{23}H_{25}FN_2S_2$) C, H, N, F, S.

5.3.10. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(fluoro) phenyl]-1-[2-(methylthio)phenyl]-1*H*-pyrrole (11)

White needles (yield 25%), mp 127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.25 (m, 1H), 7.12–7.08 (m, 5H), 6.79–6.75 (m, 2H), 6.33 (s, 1H), 3.48 (s, 2H), 2.79–2.75 (m, 4H), 2.72–2.68 (m, 4H), 2.35 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.19, 22.27, 28.33, 49.20, 55.37, 114.08, 114.32, 118.70, 119.85, 124.69, 127.90, 128.30, 129.61, 130.28, 131.33, 135.18, 136.40, 138.28, 159.22, 163.60. Anal. ($C_{23}H_{25}FN_2S_2$) C, H, N, F, S.

5.3.11. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(methylthio)phenyl]-1-[4-(fluoro)phenyl]1*H*-pyrrole (12)

White needles (yield 68%). Analytical data, mp, and ^{1}H NMR spectrum were consistent with literature.[22]

5.3.12. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(fluoro) phenyl]-1-[4-(methylthio)phenyl]-1*H*-pyrrole (13)

White needles (yield 44%), mp 153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 7.27 Hz, 2H), 7.12–7.08 (m, 4H), 7.03–7.00 (m, J = 7.27 Hz, 2H), 6.35 (s, 1H), 3.54 (s, 2H), 2.82–2.78 (m, 4H), 2.75–2.73 (m, 4H), 2.38 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.29, 22.29, 28.55, 49.22, 55.50, 114.10, 114.27, 119.33, 120.31, 124.11, 128.55, 129.23, 131.41, 134.20, 136.70, 138.62, 158.11, 161.02. Anal. ($C_{23}H_{25}FN_2S_2$) C, H, N, F, S.

5.3.13. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(methyl)phenyl]-1-[4-(methoxy)phenyl]-1*H*-pyrrole (14)

White needles (yield 15%), mp 128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 7.27 Hz, 2H), 6.96–6.92 (m, 4H), 6.88 (d, J = 7.27 Hz, 2H), 6.28 (s, 1H), 3.82 (s, 3H), 3.47 (s, 2H), 2.80–2.77 (m, 4H), 2.69–2.66 (m, 4H), 2.25 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.29, 24.29, 28.55, 49.22, 55.50, 55.90, 114.00, 114.17, 119.35, 122.34, 124.11, 128.55, 129.23, 131.41, 134.20, 135.44, 136.70, 138.62. Anal. ($C_{24}H_{28}N_2OS$) C, H, N, S.

5.3.14. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(methoxy)phenyl]-1-[4-(methyl)phenyl]-1*H*-pyrrole (15)

White needles (yield 45%), mp 127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 7.27 Hz, 2H), 7.03 (d, J = 7.27 Hz, 2H), 6.98–6.94 (m, 4H), 6.29 (s, 1H), 3.80 (s, 3H), 3.47 (s, 2H), 2.82–2.78 (m, 4H), 2.72–2.70 (m, 4H), 2.25–2.23 (m, 3H), 2.05 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.34, 24.30, 28.57, 49.25, 55.56, 55.99,

114.09, 114.23, 119.33, 120.21, 124.51, 127.33, 128.15, 129.23, 131.46, 134.10, 135.70, 136.22. Anal. ($C_{24}H_{28}N_2OS$) C, H, N, S.

5.3.15. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(ethyl) phenyl]-1-[4-(methoxy)phenyl]-1*H*-pyrrole (16)

White needles (yield 25%), mp 92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 7.27 Hz, 2H), 6.97 (s, 4H), 6.86 (d, J = 7.27 Hz, 2H), 6.29 (s, 1H), 3.83 (s, 3H), 3.49 (s, 2H), 2.58–2.56 (m, 4H), 2.54–2.53 (m, 4H), 2.40 (q, J = 7.1 Hz, 2H), 2.04 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.34, 14.30, 28.57, 32.19, 49.25, 55.56, 55.99, 114.06, 114.13, 119.43, 120.31, 124.51, 127.30, 128.25, 129.33, 131.40, 134.20, 135.70, 137.02. Anal. ($C_{25}H_{30}N_2OS$) C, H, N, S.

5.3.16. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(meth-oxy)phenyl]-1-[4-(ethyl)phenyl]-1*H*-pyrrole (17)

White needles (yield 35%), mp 105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 7.27 Hz, 2H), 7.03 (d, J = 7.27 Hz, 2H), 6.97 (d, J = 7.27 Hz, 2H), 6.67 (d, J = 7.27 Hz, 2H), 6.24 (s, 1H), 3.73 (s, 3H), 3.47 (s, 2H), 2.82–2.78 (m, 4H), 2.74–2.70 (m, 6H), 2.05 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.30, 14.29, 28.60, 32.21, 49.28, 55.60, 60.09, 114.00, 114.11, 119.23, 120.21, 124.41, 127.40, 128.44, 129.33, 131.10, 134.38, 135.22, 137.19. Anal. ($C_{25}H_{30}N_2OS$) C, H, N, S.

5.3.17. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(propyl) phenyl]-1-[4-(methoxy)phenyl]-1*H*-pyrrole (18)

White needles (yield 35%), mp 127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 7.27 Hz, 2H), 6.98–6.93 (m, 6H), 6.29 (s, 1H), 3.83 (s, 3H), 3.46 (s, 2H), 2.80–2.76 (m, 4H), 2.73–2.70 (m, 4H), 2.43 (t, J = 7.1 Hz, 2H), 2.04 (s, 3H), 1.64–1.62 (m, 2H), 0.91 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.30, 13.29, 24.56, 28.60, 38.21, 49.28, 55.60, 60.09, 113.98, 114.08, 119.03, 121.34, 125.41, 127.40, 128.24, 129.53, 131.15, 134.38, 135.00, 137.33. Anal. ($C_{26}H_{32}N_2OS$) C, H, N, S.

5.3.18. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(meth-oxy)phenyl]-1-[4-(propyl)phenyl]-1*H*-pyrrole (19)

White needles (yield 25%), mp 105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 7.27 Hz, 2H), 7.05 (d, J = 7.27 Hz, 2H), 6.92 (s, 4H), 6.29 (s, 1H), 3.81 (s, 3H), 3.48 (s, 2H), 2.80–2.78 (m, 4H), 2.74–2.71 (m, 4H), 2.60 (t, J = 7.1 Hz, 2H), 2.05 (s, 3H), 1.67–1.64 (m, 2H), 0.94 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.30, 13.33, 24.40, 28.40, 38.33, 49.50, 55.55, 60.00, 113.98, 114.08, 120.03, 122.34, 125.40, 126.80, 128.94, 129.73, 130.05, 134.28, 135.01, 136.77. Anal. ($C_{26}H_{32}N_2OS$) C, H, N, S.

5.3.19. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(*i*-pro-pyl)phenyl]-1-[4-(methoxy)phenyl]-1*H*-pyrrole (20)

White needles (yield 40%), mp 122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 7.27 Hz, 2H), 6.98 (s, 4H), 6.87 (d, J = 7.27 Hz, 2H), 6.29 (s, 1H), 3.83 (s, 3H), 3.46 (s, 2H), 2.89–2.86 (m, 5H), 2.76–2.73 (m, 4H), 2.03 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H)). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.30, 23.44, 28.40, 36.33, 49.50, 55.55, 59.40, 113.98, 114.09, 120.00, 122.34, 125.40, 128.94, 129.73, 130.08, 134.26, 135.11, 136.78, 148.66. Anal. ($C_{26}H_{32}N_2OS$) C, H, N, S.

5.3.20. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(meth-oxy)phenyl]-1-[4-(*i*-propyl)phenyl]-1*H*-pyrrole (21)

White needles (yield 20%), mp 118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 7.27 Hz, 2H), 7.05 (d, J = 7.27 Hz, 2H), 6.95–6.90 (m, 4H), 6.28 (s, 1H), 3.85 (s, 3H), 3.48 (s, 2H), 2.94–2.90 (m, 1H), 2.82–2.78 (m, 4H), 2.74–2.70 (m, 4H), 2.06 (s, 3H), 1.27 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.30, 23.66, 28.43, 36.40, 49.39, 55.60, 59.41, 114.08, 114.09, 120.00, 122.34, 125.40, 128.90, 129.73, 131.22, 134.26, 135.11, 136.78, 148.69. Anal. ($C_{26}H_{32}N_2OS$) C, H, N, S.

5.3.21. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(meth-yl)phenyl]-1-[4-(methylthio)phenyl]-1*H*-pyrrole (22)

White needles (yield 60%), mp 153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 7.27 Hz, 2H), 7.13 (d, J = 7.27 Hz, 2H), 6.94 (s, 4H), 6.30 (s, 1H), 3.45 (s, 2H), 2.85–2.80 (m, 4H), 2.78–2.74 (m, 4H), 2.49 (s, 3H), 2.25 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.30, 15.00, 24.43, 28.35, 49.39, 55.60, 114.05, 114.17, 120.33, 121.99, 125.40, 128.90, 129.73, 131.23, 134.27, 135.20, 136.78, 137.69. Anal. ($C_{24}H_{28}N_2S_2$) C, H, N, S.

5.3.22. 2-Methyl–3-[(thiomorpholin-4-yl)-methyl]-5-[4-(meth-ylthio)phenyl]-1-[4-(methyl)phenyl]1*H*-pyrrole (23)

White needles (yield 30%) mp 162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 7.27 Hz, 2H), 7.06–7.00 (m, 6H), 6.30 (s, 1H), 3.46 (s, 2H), 2.79–2.76 (m, 4H), 2.72–2.69 (m, 4H), 2.41 (s, 3H), 2.38 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.33, 14.40, 24.39, 28.40, 49.41, 55.57, 114.02, 114.25, 120.33, 122.18, 125.34, 128.97, 129.78, 131.11, 134.29, 136.10, 136.81, 137.69. Anal. ($C_{24}H_{28}N_2S_2$) C, H, N, S.

5.3.23. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(ethyl) phenyl]-1-[4-(methylthio)phenyl]-1*H*-pyrrole (24)

White needles (yield 35%), mp 112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 7.27 Hz, 2H), 7.06 (d, J = 7.27 Hz, 2H), 6.99–6.96 (m, 4H), 6.27 (s, 1H), 3.47 (s, 2H), 2.84–2.80 (m, 4H), 2.78–2.76 (m, 4H), 2.55 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 2.05 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.33, 14.40, 22.44, 32.39, 28.40, 49.41, 55.57, 114.02, 114.25, 120.33, 122.37, 125.34, 127.99, 128.78, 131.11, 134.29, 135.10, 136.21, 136.56. Anal. ($C_{25}H_{30}N_2S_2$) C, H, N, S.

5.3.24. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(meth-ylthio)phenyl]-1-[4-(ethyl)phenyl]-1*H*-pyrrole (25)

White needles (yield 35%), mp 168 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 7.27 Hz, 2H), 7.04–7.00 (m, 6H), 6.31 (s, 1H), 3.47 (s, 2H), 2.84–2.80 (m, 4H), 2.75–2.70 (m, 6H), 2.42 (s, 3H), 2.05 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.39, 14.42, 22.43, 32.40, 28.30, 49.43, 55.51, 114.09, 114.33, 121.30, 122.55, 124.74, 128.99, 130.07, 131.10, 134.29, 135.10, 136.11, 136.33. Anal. ($C_{25}H_{30}N_2S_2$) C, H, N, S.

5.3.25. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(propyl) phenyl]-1-[4-(methylthio)phenyl]-1*H*-pyrrole (26)

White needles (yield 45%), mp 125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 7.27 Hz, 2H), 7.06 (d, J = 7.27 Hz, 2H), 6.98–6.93 (m, 4H), 6.29 (s, 1H), 3.46 (s, 2H), 2.79–2.76 (m, 4H), 2.72–2.69 (m, 4H), 2.54–2.50 (m, 5H), 2.05 (s, 3H), 1.59–1.56 (m, 2H), 0.91 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.39, 13.78, 22.39, 24.34, 38.31, 28.33, 49.41, 55.49, 114.12, 114.55, 121.31, 122.01, 125.41, 128.92, 131.02, 131.10, 134.32, 135.22, 136.15, 137.93. Anal. ($C_{26}H_{32}N_2S_2$) C, H, N, S.

5.3.26. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(meth-ylthio)phenyl]-1-[4-(propyl)phenyl]-1*H*-pyrrole (27)

Yellow oil (yield 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 7.27 Hz, 2H), 7.04–7.00 (m, 6H), 6.31 (s, 1H), 3.47 (s, 2H), 2.80–2.76 (m, 4H), 2.74–2.70 (m, 4H), 2.61 (t, J = 7.1 Hz, 2H), 2.40 (s, 3H), 2.05 (s, 3H), 1.68–1.63 (m, 2H), 0.93 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.33, 13.81, 22.37, 24.32, 38.30, 28.39, 49.50, 55.50, 114.11, 114.18, 121.30, 122.21, 126.21, 127.72,

130.32, 131.70, 134.52, 135.00, 136.21, 138.00. Anal. ($C_{26}H_{32}N_2S_2$) C, H, N, S.

5.3.27. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(*i*-propyl)phenyl]-1-[4-(methylthio)phenyl]-1*H*-pyrrole (28)

White needles (yield 60%), mp 131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 7.27 Hz, 2H), 7.07 (d, J = 7.27 Hz, 2H), 6.92–6.90 (m, 4H), 6.28 (s, 1H), 3.49 (s, 2H), 2.92–2.89 (m, 1H), 2.87–2.81 (m, 4H), 2.74–2.72 (m, 4H), 2.38 (s, 3H), 2.06 (s, 3H), 1.27 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.33, 22.43, 23.41, 36.30, 28.39, 49.50, 55.50, 114.09, 114.11, 122.01, 125.03, 126.55, 127.72, 131.69, 135.02, 135.40, 136.22, 138.03, 147.77. Anal. ($C_{26}H_{32}N_2S_2$) C, H, N, S.

5.3.28. 2-Methyl-3-[(thiomorpholin-4-yl)-methyl]-5-[4-(methylthio)phenyl]-1-[4-(*i*-propyl)phenyl]-1*H*-pyrrole (29)

Yellow oil (yield 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 7.27 Hz, 2H), 7.04–7.00 (m, 6H), 6.31 (s, 1H), 3.49 (s, 2H), 2.78–2.80 (m,1H), 2.76–2.72 (m, 4H), 2.70–2.68 (m, 4H), 2.41 (s, 3H), 2.06 (s, 3H), 1.28 (s, 3H), 1.23 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.30, 22.32, 23.39, 36.22, 28.41, 49.67, 55.61, 114.01, 114.33, 122.05, 123.63, 127.05, 127.70, 131.29, 135.12, 135.37, 136.10, 138.00, 148.01. Anal. ($C_{26}H_{32}N_2S_2$) C, H, N, S.

Acknowledgment

We are grateful for financial support from CARIPLO Foundation (Rif. 2006.0880/10.8485 Bando 2006) and from Istituto Pasteur-Fondazione Cenci Bolognetti.

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