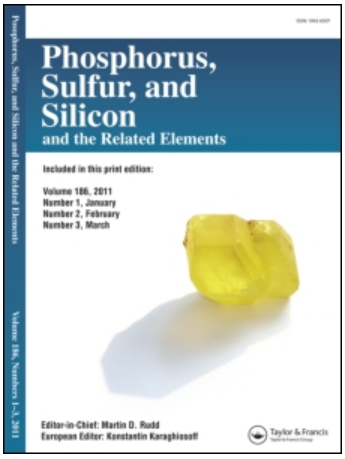

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis and Biological Evaluation of Novel Tetracyclic Benzothiazepines

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Online publication date: 23 March 2010

To cite this Article Apparao, T. , Peesapati, V. , Rupavani, G. and Ramakrishna, S.(2010) 'Synthesis and Biological Evaluation of Novel Tetracyclic Benzothiazepines', Phosphorus, Sulfur, and Silicon and the Related Elements, 185: 4, 697 — 704
To link to this Article: DOI: 10.1080/10426500902922917
URL: http://dx.doi.org/10.1080/10426500902922917

Phosphorus, Sulfur, and Silicon, 185:697–704, 2010

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500902922917

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SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL TETRACYCLIC BENZOTHIAZEPINES

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6-Arylidene-2,3-dimethyl-6,7,8,9-tetrahydro-benzocyclohepten-5-one 2a–l were obtained by the condensation of 2,3-dimethyl/3-methyl benzocyclohepten-5-one 1 with appropriate aromatic aldehydes, and upon condensation with 2-aminothiophenol in ethyl alcohol yielded 1,5-benzothiazepine derivatives 3a–l, respectively. Compounds 3d and 3h were found to possess antimicrobial activity when tested against* B. Subtilis*. Compounds 3i and 3j were found to possess moderate anti-inflammatory activity. Compound 3b was found to possess comparable antifungal activity when compared to clotrimazole against* Trichomonas *species.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Antibacterial, anti-inflammatory, and antifungal activities; aromatic aldehydes; benzocyclohepten-5-one; 1,5-benzothiazepines

INTRODUCTION

The synthesis of benzothiazepines constitutes an important area of research with a large number of 1,5-benzothiazepines[1] exhibiting a variety of pharmacological activities. However, their derivatives belong to the most frequently studied moieties. The 1,5-benzothiazepine derivatives are of particular interest for lead discovery because they have been found to be active against different families of targets.[2] The 1,5-benzothiazepine scaffold has been used as cardiovascular modulator[3] such as vasodilator[4,5] and antiarrythmic,[6] protease inhibitors,[7] elastase[8]/ACE inhibitors,[9] antagonists of several G-protein coupled receptors such as cholecystokinin (CCK) receptor,[10] and as interleukin-1b converting enzyme inhibitors[7]/the angiotensin II receptor (ACE) inhibitors.[11] Recently, anticancer activity,[12,13] hemodynamic effects,[14] antihypertensive activity,[15,16] antiulcer activity,[17,18] and spasmolytic activities[19–23] have also been reported. The first molecule used clinically was diltiazem, followed by clentiazem, for their cardiovascular action.[4,24,25] Some of the 1,5-benzothiazepine derivatives, which includes thiazesim and quetiapine fumarate,[26,27] have

Received 9 January 2009; accepted 24 March 2009.
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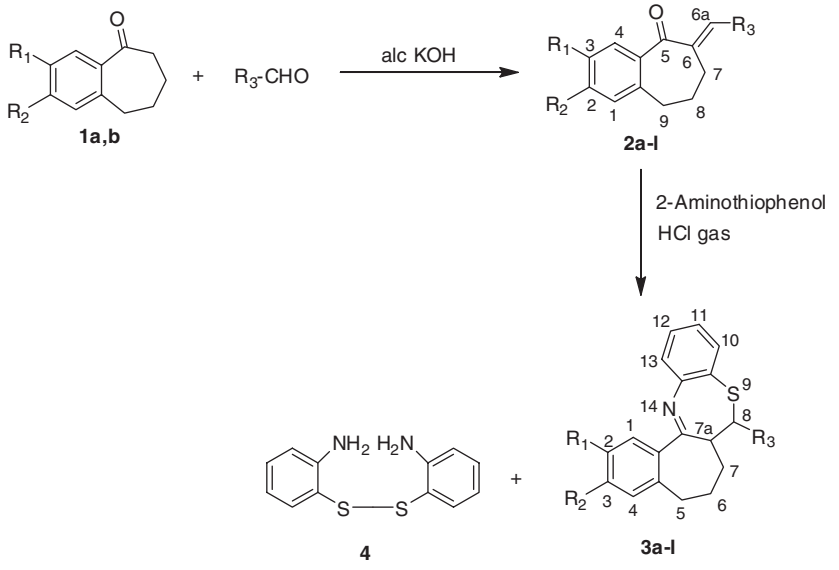
also been used clinically for CNS disorders, Prompted by these observations and in continuation of our interest in the synthesis of biologically active fused heterocyclics,[28–31] we report in this article the synthesis, structure determination, and primary biological screening of new benzothiazepines **3a–l**. This method is a most satisfactory simple, one-pot operation and provides consistently with moderate yields.

RESULTS AND DISCUSSION

6-Arylidene-2,3-dimethyl/3-methyl-6,7,8,9-tetrahydro-benzocyclohepten-5-one **2a** is a useful intermediate for the formation of into new heterocycles. 6-Arylidene-2,3-dimethyl/3-methyl-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-ones **2a** were obtained by the condensation of 2,3-dimethylbenzocyclohepten-5-one[32] **1a** with appropriate



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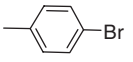
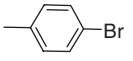
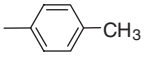
1b) R_1= CH_3, R_2 = H

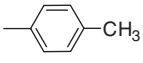
2a&3a) R_1 & R_2 = CH_3, R_3 = 

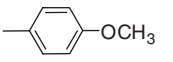
2b&3b) R_1 = CH_3, R_2 = H, R_3 = 

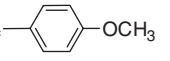
2c&3c) R_1 & R_2 = CH_3, R_3 = 

2d&3d) R_1 = CH_3, R_2 = H, R_3 = 

2e&3e) R_1 & R_2 =CH_3, R_3 = 

2f&3f) R_1 = CH_3, R_2 = H, R_3 = 

2g&3g) R_1 & R_2 = CH_3, R_3 = 

2h&3h) R_1 = CH_3, R_2 = H, R_3 = 

2i&3i) R_1& R_2 = CH_3, R_3 = 

2j&3j) R_1 = CH_3, R_2 = H, R_3 = 

2k&3k) R_1 & R_2 =CH_3, , R_3 = 

2l&3l) R_1 = CH_3, R_2 = H, R_3 = 

Scheme 1 Synthesis of 1,5-benzothiazepine derivatives.

aldehydes. In the enone **2a**, the olefinic proton = CH−Ar appeared at δ 7.85–7.95 in the ^{1}H NMR spectra. The 6-aryl methylene derivatives **2a–l** reacted with 2-aminothiophenol in dry ethanol and dry HCl gas was passed with the reaction mixture until it was saturated. The usual workup gave 2,3-dimethyl-8-phenyl-6,7,7a,8-tetrahydro-5H-9-thia-14-aza-dibenzo[a,i]heptalene**s 3a–l** along with a small amount of a dimer **4** as a side product (Scheme 1). One can control or minimize the formation of disulfide (dimer) **4** by saturating the reaction mixture with HCl gas before adding the 2-aminothiophenol. The mass spectra and ^{1}H NMR spectral data gave strong substantiation for the structure of **3a**. The mass spectrum of **3a** (taken as a representative example) had the molecular ion peaks at *m/z* 463 (4%), 420 (22%), 418 (20%), 292 (11%), 266 (38%), 253 (100%), 251 (22%), 128 (12%), 115 (18%), 91 (13%), consistent with the molecular formula. The ^{1}H NMR spectrum of **3a** showed the presence of a doublet and a multiplet at δ 4.30–4.34 (J = 7.25 Hz) and δ 3.00–3.15, respectively, integrating for one proton each**,** assigned to C_8−H proton and C_{7a}−H proton, respectively. Further, the spectrum had signals for 3-methylene groups between 1.45 and 2.95. The aromatic protons appeared as a multiplet at 6.90–7.60. The ^{13}C NMR spectrum is also in agreement with proposed structure **3a**. The IR spectrum also showed the disappearance of the carbonyl absorption band and the presence of −C=N− group in the region 1618 cm^{-1}, indicating the cyclization had taken place (Tables I and II).

Table I IR (cm^{-1}), ^{1}H NMR (δ ppm), and mass of the compounds **2a–l**

Compd.	C=C− stretch	^{1}H NMR ($CDCl_3$)	MS(EI): *m/z* (M^+)
2a	1601	δ 1.95–2.10 (2H, m, 8-CH_2), 2.38 (6H, s, 2-CH_3). 2.70 (2H, t, 7-CH_2). 2.85 (2H, t, 9-CH_2).7.00–7.75 (6H, m), 7.85–7.95 (1H, s, C=CH).	355
2b	1595	δ 1.80–2.00 (2H, m, 8-CH_2), 2.40 (3H, s, CH_3). 2.30 (2H, t, 7-CH_2). 2.80 (2H, t, 9-CH_2).7.00–7.70 (7H, m), 7.75 (1H, s, C=CH).	342
2c	1616	δ 1.90–2.00 (2H, m, 8-CH_2), 2.30 (6H, s, 2CH_3). 2.20 (2H, t, 7-CH_2). 2.80 (2H, t, 9-CH_2).7.00–7.65 (7H, m), 7.70 (1H, s, C=CH).	276
2d	1601	δ 1.80–2.00 (2H, m, 8-CH_2), 2.35 (3H, s, 2CH_3). 2.25 (2H, t, 7-CH_2). 2.60 (2H, t, 9-CH_2).7.00–7.70 (8H, m), 7.75 (1H, s, C=CH).	262
2e	1595	δ 1.90–2.00 (2H, m, 8-CH_2), 2.40 (9H, s, 3CH_3). 2.40 (2H, t, 7-CH_2). 2.50 (2H, t, 9-CH_2).6.95–7.60 (8H, m, aromatic), 7.65 (1H, s, C=CH).	276
2f	1593	δ 1.78–2.00 (2H, m, 8-CH_2), 2.30 (6H, s, 2CH_3). 2.20 (2H, t, 7-CH_2). 2.70 (2H, t, 9-CH_2), 6.90–7.50 (8H, m), 7.70 (1H, s, C=CH).	262
2g	1590	δ 1.75–2. 00 (2H, m, 8-CH_2), 2.40 (6H, s, 2CH_3). 3.5 (H, s, OCH_3) 2.70 (2H, t, 7-CH_2). 2.85 (2H, t, 9-CH_2).7.00–7.75 (8H, m,), 7.80 (1H, s, C=CH).	290
2h	1588	δ 1.70–2.00 (2H, m, 8-CH_2), 2.40 (3H, s, CH_3). 2.24 (2H, t, 7-CH_2). 2.60 (2H, t, 9-CH_2). 3.6 (H, s, OCH_3) 6.80–7.40 (7H, m,), 7.70 (1H, s, C=CH).	276
2i	1610	δ 1.65–2.00 (2H, m, 8-CH_2), 2.30 (6H, s, 2CH_3). 2.40 (2H, t, 7-CH_2). 2.60 (2H, t, 9-CH_2). 6.60–7.30 (5H, m,), 7.60 (1H, s, C=CH).	282
2j	1590	δ 1.70–2.00 (2H, m, 8-CH_2), 2.40 (3H, s, CH_3), 2.40 (2H, t, 7-CH_2), 2.60 (2H, t, 9-CH_2), 6.65–7.35 (6H, m), 7.60 (1H, s, C=CH).	268
2k	1580	δ 1.80–2.00 (2H, m, 8-CH_2), 2.30 (6H, s, 2CH_3). 2.40 (2H, t, 7-CH_2). 2.50 (2H, t, 9-CH_2).6.70–7.60 (5H, m), 7.70 (1H, s, C=CH).	266
2l	1593	δ 1.80–2.20 (2H, m, 8-CH_2), 2.30 (3H, s, CH_3). 2.50 (2H, t, 7-CH_2), 2.70 (2H, t, 9-CH_2), 6.80–7.50 (6H, m), 7.70 (1H, s, C=CH).	252
		^{13}C NMR of compound 2a	
2a		19.2, 23.7 (C-8), 28.3 (C-7), 32.4 (C-9), 124.2–136.8 (Aromatic protons) 133.4 (C-6) 135.2 C-6a), 194.5 (C=O)	

Table II IR (cm^{-1}), ^1H NMR (δ ppm), and mass of the compounds

Compd.	C=N	^{1}HNMR ($CDCl_3$)	MS (EI): m/z (M^+)
3a	1618	δ 1.45–1.60 (2H, m, 6-CH_2), 2.15 & 2.30 (6H, 2s, CH_3), 2.70–2.80 (2H, m, 7-CH_2), 2.85–2.95 (2H, t, 5-CH_2), 3.00–3.15 (1H, m, 7a-CH), 4.30 (1H, d, 8-CH, $J = 7.25$ Hz), 6.90–7.60 (10H, m).	463
3b	1621	δ 1.60–1.80 (1H, m, 6-CH_2), 2.40 (3H, s, CH_3), 2.65–2.75 (2H, t, 7-CH_2), 2.80–2.95 (2H, t, 5-CH_2), 3.05–3.12 (1H, m, 7a-CH), 4.30 (1H, d, 8-CH, $J = 7.25$ Hz), 6.90–7.60 (11H, m).	447
3c	1660	δ 1.45–1.60 (2H, m, 6-CH_2), 2.45 (6H, 2s, $2CH_3$), 2.70–2.80 (2H, m, 7-CH_2), 2.85–2.95 (2H, t, 5-CH_2), 3.10–3.20 (1H, m, 7a-CH), 4.30 (1H, d, 8-CH, $J = 7.25$ Hz), 7.00–7.85 (11H, m).	369
3d	1690	δ 1.50–1.80 (2H, m, 6-CH_2), 2.45 (3H, s-CH_3), 2.62–2.85 (2H, m, 7-CH_2), 2.90–3.00 (2H, t, 5-CH_2), 3.00–3.15 (1H, m, 7a-CH), 4.40 (1H, d, 8-CH, $J = 7.30$ Hz), 6.95–7.60 (12H, m):	383
3e	1695	δ 1.56–1.70 (2H, m, 6-CH_2), 2.26–2.30 (9H, 3s, 3x, CH_3), 2.72–2.74 (2H, m, 7-CH_2), 2.78–2.88 (2H, t, 5-CH_2), 3.12–3.30 (1H, m, 7a-CH), 4.31–4.34 (1H, d, 8-CH**,** $J = 7.28$, Hz), 6.70–7.53 (10H, m).	397
3f	1688	δ 1.50–1.75 (2H, m, 6-CH_2), 2.20–2.45 (6H, 2s, 2x-CH_3), 2.65–2.75 (2H, m, 7-CH_2), 2.80–2.95 (2H, t, 5-CH_2), 3.02–3.15 (1H, m, 7a-CH), 4.35 (1H, d, 8-CH, $J = 7.26$ Hz), 6.90–7.75 (11H, m).	383
3g	1680	δ 1.60–1.80 (2H, m, 6-CH_2), 2.29 (6H, 2s, 2-CH_3), 2.88–2.95 (2H, m, 5-CH_2), 3.10–3.20 (1H, m, 7a-CH), 3.80 (3H, s, -OCH_3), 4.40 (1H, d, 8-CH, $J = 7.30$ Hz); 6.90–7.70 (10H, m).	413
3h	1695	δ 1.70–1.90 (2H, m, 6-CH_2), 2.40 (3H, s, -CH_3), 2.65–2.75 (2H, m, 7-CH_2), 2.80–2.95 (2H, t, 5-CH_2), 3.05–3.20 (1H, m, 7a-CH), 3.80(3H, s, -OCH_3), 4.55 (1H, d, 8-CH $J = 7.28$ Hz), 6.90–7.70 (11H, m).	399
3i	1688	δ 1.75–1.90 (2H, m, 6-CH_2), 2.30 (6H, s, 2-CH_3), 2.65–2.75 (2H, t, 7-CH_2), 2.80–2.95 (2H, t, 5-CH_2), 3.15–3.25 (1H, m, 7a-CH), 4.45 (1H, d, 8-CH, $J = 7.32$ Hz); 6.95–7.50 (9H, m).	389
3j	1682	δ 1.65–1.90 (2H, m, 6-CH_2), 2.35 (3H, s, -CH_3), 2.65–2.80 (2H, m, 7-CH_2), 2.80–2.90 (2H, t, 5-CH_2), 3.00–3.12 (1H, m, 7a-CH), 4.60 (1H, d, 8CH, $J = 7.32$ Hz); 6.95–7.50 (10H, m).	375
3k	1670	δ 1.30–1.75 (2H, m, 6-CH_2), 2.32 (3H, s, -CH_3), 2.60–2.70 (2H, m, 7-CH_2), 2.75–2.85 (2H, t, 5-CH_2), 3.00–3.15 (1H, m, 7a-CH), 4.35 (1H, d, 8CH, $J = 7.30$ Hz), 6.90–7.50 (9H, m).	373
3l	1685	1.50–1.75 (2H, m, 6-CH_2), 2.35 (3H, s, -CH_3), 2.60–2.80 (2H, m, 7-CH_2), 2.85–2.95 (2H, t, 5-CH_2), 3.10–3.20 (1H, m, 7a-CH), 4.70 (1H, d, 8-CH, $J = 7.32$ Hz), 6.90–7.50 (10H, m).	359
4	3400	δ 4.70 (4H, s, 6–2x-NH_2), 6.40–6.70 (4H, m), 7.00–7.20 (4H, m).	248
		C^{13} NMR of compound 3a	
3a		δ 19.6, 26.2 (C-6), 29.2 (C-7), 33.4 (C-5), 41.6 (C-7a), 53.6 (C-8), 118.2–136.5 (Aromatic protons), 160.2 (C=N).	

Under analogous conditions, the reaction of 6-arylidene-2,3-dimethyl/3-methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one **2b–l** with 2-aminothiophenol in ethyl alcohol afforded 1,5-benzothiazepine derivatives **3b**-**l**, respectively.

CONCLUSION

In summary, this work demonstrates an efficient and convenient method for synthesis of 1,5-benzothiazepines and their biological activities evaluated. The results showed that

most of the compounds exhibited moderate to good activity against *Trichomonas viginalis* and also displayed the anti-inflammatory activity and antibacterial activity.

BIOLOGICAL EVALUATION

The new compounds were characterized from their spectral data and elemental analysis and were screened for their antibacterial activity, anti-inflammatory activity, and antifungal activity (see the Supplemental Materials available online, Figures S1 and S2, Table S1).

Antibacterial Activity

The minimum inhibitory concentration was done by the broth dilution method according to the method of Villanova 1982.[33]

Anti-Inflammatory Activity

The anti-inflammatory activity of the test compounds was evaluated in Wistar rats employing the method of Winter et al.[34]

Antifungal Activity

The antifungal activity was tested against *Trichmonas vaginalis*.

EXPERIMENTAL

Melting points were determined using Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a FT-IR 1605 Perkin-Elmer. ^{1}H NMR were taken in $CDCl_3$ on a Varian FT-80A spectrometer with TMS as an internal standard and mass spectra on a VG-Micro mass 7070H mass spectrometer. TLC was run on silica gel G coated plates and iodine vapor as visualizing agent.

General Experimental Procedure (2a–l): Synthesis of 6-Arylidene-2,3-dimethyl-6,7,8,9-tetrahydro-benzocyclohepten-5-one (2a)

A mixture of 2,3-dimethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one **1a** (0.35 g, 2 mmol) and bromobenzaldelyde (0.20 g, 2 mmol) in ethanolic potassium hydroxide was stirred at room temperature for 30 min. During this time, the product was formed. The reaction mixture was neutralized with aqueous acetic acid 5–6 mL. The solid thus obtained was filtered and washed thoroughly with water and dried. Recrystallization from methanol gave the product **2a** (0.5 g, 92%) as colorless crystals (Table III).

Analogues **2b–l** were similarly obtained using the same procedure. The structures of all the compounds were established on the basis of spectral data and elemental analysis.

General Experimental Procedure (3a–l): Synthesis of 4-(2,3-Dimethyl-6,7,7a,8-tetrahydro-5H-benzo[b]benzo[3,4]cyclo-hepta[e][1,4]thiazepin-8-yl]-benzene (3a)

6-Arylidene-2,3-dimethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one **2a** (0.52 g, 2 mmol) was dissolved in dry ethanol (8 mL) and was saturated with HCl gas followed

Table III Physical and analytical data of the newly synthesized compounds **3a–l**

Compound	Mp [°C]	Yield [%]	Mol. Formula (Mol. Wt.)	Analyses% require (found)			
				C	H	N	S
2a	112–114	92	$C_{20}H_{19}BrO$ (354)	67.79 (67.61)	5.36 (5.39)		
2b	124–125	90	$C_{19}H_{17}BrO$ (340)	66.86 (67.05)	4.98 (5.00)		
2c	130–131	95	$C_{20}H_{20}O$ (276)	86.79 (86.95)	7.23 (7.24)		
2d	112–114	94	$C_{19}H_{18}O$ (262)	86.69 (87.02)	4.98 (5.00)		
2e	82–84	96	$C_{21}H_{22}O_2$ (306)	86.89 (86.59)	7.58 (7.56)		
2f	90–92	95	$C_{20}H_{20}O_2$ (292)	86.95 (86.64)	7.24 (7.22)		
2g	86–88	94	$C_{21}H_{22}O$ (290)	86.95 (86.64)	7.24 (7.22)		
2h	110–112	97	$C_{20}H_{20}O$ (276)	87.02 (86.69)	6.80 (6.84)		
2i	192–194	80	$C_{18}H_{18}OS$ (282)	76.59 (76.47)	6.38 (6.24)		
2j	135–137	75	$C_{17}H_{17}OS$ (268)	76.59 (76.47)	6.05 (6.10)		
2k	150–152	82	$C_{18}H_{16}O_2$ (266)	81.20 (81.13)	6.76 (6.81)		
2l	108–110	74	$C_{17}H_{16}O_2$ (252)	80.95 (80.90)	6.39 (6.34)		
3a	140–141	65	$C_{26}H_{24}BrNS$ (461)	67.53 (67.42)	5.23 (5.20)	3.79 (3.83)	6.92 (6.89)
3b	138–140	63	$C_{25}H_{22}BrNS$ (447)	66.90 (66.84)	4.95 (4.98)	3.12 (3.10)	7.10 (7.09)
3c	190–192	65	$C_{26}H_{25}NS$ (383)	81.26 (81.20)	6.25 (6.23)	3.78 (3.80)	8.68 (8.72)
3d	186–188	60	$C_{25}H_{23}NS$ (369)	81.45 (81.50)	6.57 (6.60)	3.65 (3.68)	8.36 (8.40)
3e	132–134	58	$C_{27}H_{27}NS$ (397)	81.57 (81.54)	6.85 (6.83)	3.52 (3.50)	8.07 (8.10)
3f	204–206	60	$C_{26}H_{25}NS$ (383)	81.42 (81.39)	6.58 (6.60)	3.64 (3.66)	8.37 (8.40)
3g	192–193	59	$C_{27}H_{27}NOS$ (413)	78.40 (78.38)	6.59 (6.57)	3.40 (3.38)	7.74 (7.71)
3h	195–197	55	$C_{26}H_{25}NOS$ (399)	78.18 (78.14)	6.30 (6.26)	3.61 (3.59)	8.02 (8.00)
3i	182–184	57	$C_{24}H_{23}NS_2$ (389)	73.98 (74.02)	5.94 (5.96)	3.60 (3.62)	16.44 (16.46)
3j	178–180	58	$C_{23}H_{21}NS_2$ (375)	73.50 (73.48)	5.64 (5.62)	3.73 (3.71)	17.08 (17.10)
3k	175–177	55	$C_{24}H_{25}NOS$ (373)	77.17 (77.13)	6.20 (6.22)	3.75 (3.73)	8.58 (8.56)
3l	173–175	60	$C_{23}H_{21}NOS$ (359)	76.84 (76.78)	5.88 (5.90)	3.90 (3.88)	8.92 (8.90)
4	73–75	24–28	$C_{13}H_{14}N_2S_2$ (248)	58.02 (58.00)	4.86 (4.84)	11.26 (11.24)	25.82 (25.80)

by adding 2-aminothiophenol (0.3 mL, 3 mmol) and then refluxed for a period of 3 h. Removal of the excess of solvent under reduced pressure gave a crude solid, which was subjected to column chromatography gave two major bands. The first band was obtained in 65% yield from ethyl acetate to give light yellow crystals, and the second band was identified as a dimer (**4**) (Table III).

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