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Design and synthesis of 3-alkyl-2-aryl-1,3-thiazinan-4-one derivatives as selective cyclooxygenase (COX-2) inhibitors

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ABSTRACT

A new group of 3-alkyl-2-aryl-1,3-thiazinan-4-ones, possessing a methylsulfonyl pharmacophore, were synthesized and their biological activities were evaluated for cyclooxygenase-2 (COX-2) inhibitory activity. In vitro COX-1/COX-2 inhibition studies identified 3-benzyl-2-(4-methylsulfonylphenyl)-1,3-thiazinan-4-one (**11a**) as a potent (IC_{50} = 0.06 μM) and selective (selectivity index >285) COX-2 inhibitor.

The non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and indomethacin that act via inhibition of the cyclooxygenase (COX) enzyme, are widely used as analgesic, anti-pyretic and anti-inflammatory agents. The success of NSAIDs in treatment of various inflammatory disorders validated inhibition of COX enzyme as a highly suitable target in anti-inflammatory therapies.[1] However, the gastrointestinal toxicities associated with widespread use of NSAIDs proved to be a major problem during long term therapy. COX enzyme catalyzes the first step of the biosynthesis of PGG_2 from arachidonic acid which serves as a precursor for the synthesis of PGs, prostacyclines and thromboxanes such as TXA_2 that are collectively termed as prostanoides.[2] Nowadays, it is well established that there are at least two COX isozymes, COX-1 and COX-2.[3] The COX isoforms are heme containing enzymes that inhibit distinct expression roles in several physiological processes. The constitutive COX-1 isozyme is expressed in many tissues and appears to be important to the maintenance of physiological functions such as gastro protection and vascular homeostasis.[4] In contrast, the COX-2 isozyme is induced by stimuli such as mitogenes and oncogenes, growth factors, hormones and disorders of water-electrolyte homeostasis linking its involvement to pathological processes such as inflammation and various cancer types.[5–7] The gastrointestinal side effects associated with NSAIDs are due to the inhibition of gastroprotective PGs synthesized through the COX-1 pathway.[8,9] Thus, selective inhibition of COX-2 over COX-1 is useful for the treatment of inflammation and inflammation-associated disorders with reduced gastrointestinal toxicities when compared with NSAIDs. Recent studies have shown that the progression of Alzheimer's disease is reduced among some users of NSAIDs. Chronic treatment with selective COX-2 inhibitors may therefore slow the progress of Alzheimer's disease without causing gastrointestinal damage.[10] The majority of selective COX-2 inhibitors belong to a class of diarylheterocycles that possess vicinal diaryl substitution attached to a five- or six-membered central hetero or carbocyclic ring system (see structures **1–6** in Chart 1).[11–17] The recent termination of clinical use of some diarylheterocyclic selective COX-2 inhibitors such as rofecoxib, and valdecoxib due to their adverse cardiovascular side effects[18] clearly delineates the need to explore and evaluate new structural ring templates (scaffolds) possessing COX inhibitory activity. In addition, some studies have suggested that rofecoxib's adverse cardiac events may not be a class effect but rather an intrinsic chemical property related to its metabolism.[19] For this reason novel scaffolds with high selectivity for COX-2 inhibition need to be found and evaluated for their anti-inflammatory effects. Recently, we reported a group of 2,3-diaryl-1,3-thiazolidine-4-ones possessing a COX-2 SO_2Me pharmacophore at the *para*-position of C-2 phenyl ring in conjunction with different substituents at the *para*-position of the N-3 phenyl ring.[17] For example, 3-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)-1,3-thiazolidine-4-one (see structure **6**) exhibited highly selectivity for COX-2 inhibition. As part of our ongoing program to design new types of selective COX-2 inhibitors, we now report the design, synthesis, cyclooxygenase inhibitory and some molecular modeling studies of a new group of 3-alkyl-2-aryl-1,3-thiazinan-4-one derivatives having a six-membered

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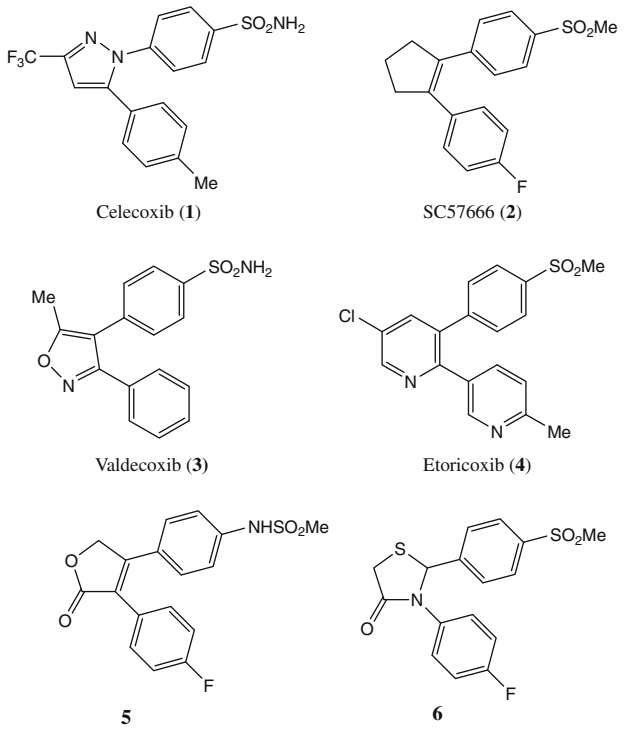
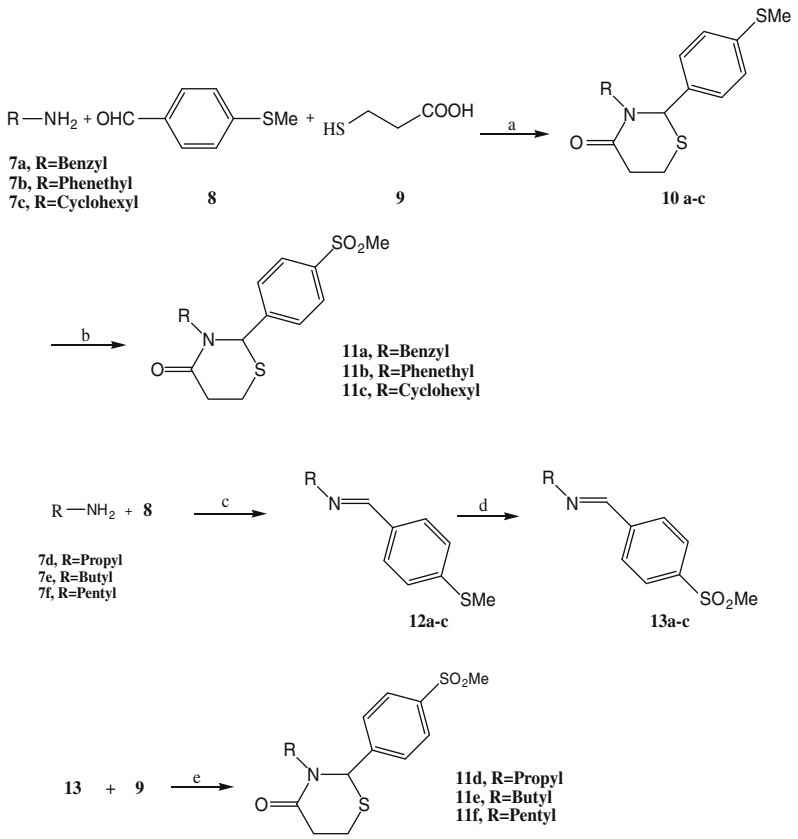


Chart 1. Representative examples of selective COX-2 inhibitors.

central ring scaffold and different alkyl or arylalkyl groups at the N-3, in order to find the effect of alkyl and arylalkyl groups on the inhibition of COX-2 activity.

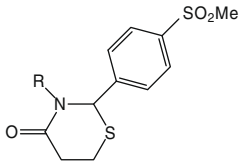
The target 3-alkyl-2-aryl-1,3-thiazinan-4-one derivatives (**11a–f**) were synthesized via the route outlined in Scheme 1. Accordingly, an appropriate amine (**7a–c)** was treated with 4-methylthiobenzaldehyde (**8**) and thioglycolic acid (**9**) in dry toluene in presence of *p*-toluenesulfonic acid under reflux to give 3-alkyl-2-(4-methylthiophenyl)-1,3-thiazinan-4-one (**10**, 10–12%).[20] Oxidation of **10** using 30% H_2O_2 in hydromethanol in the presence of a trace amount of WO_3 afforded the 3-alkyl-2-(4-methylsulfonylphenyl)-1,3-thiazinan-4-one (**11a–c**, 35–75%).[24] For low boiling point amines (**7d–f**), the intermediate imine products (**12**) were obtained by the reaction with 4-metylthiobenzaldehyde in anhydrous DMF. Subsequent oxidation **12** with hydrogen peroxide and WO_3 in hydromethanol solution afforded the (*E*)-*N*-(4-(methylsulfonylbenzylidene) alkan-1-amine (**13**).[25] Reaction of **13** and mercaptopropionicacid under refluxing in dry toluene according as described previously gave **11d–f** (12–45%).[24]

A group of 3-alkyl-2-aryl-1,3-thiazinan-4-one derivatives having different substituents at the N-3 central ring (**11a–f**) were prepared to investigate the effect of different substituents on COX-2 selectivity and potency. The ability of the 1,3-thiazinan-4-ones **11a–f** to inhibit the COX-1 and COX-2 isozymes was determined using chemiluminescent enzyme assays[21] (see enzyme inhibition data in Table 1) according to our previously reported method.[17] In vitro COX-1/COX-2 inhibition studies showed that all compounds **11a–f** were selective inhibitors of the COX-2 isozyme with IC_{50} values in the highly potent 0.06–0.11 μM range, and COX-2 selectivity indexes (S.I.) in the 128.4–285.8 range. The relative COX-2 potency, and COX-2 selectivity profiles for the 1,3-thiazinan-4-one derivatives **11a–f**, with respect to the N-3 substituent (R) was benzyl > phenethyl > pentyl > butyl > propyl. These data showed that increasing of lipophilicity of substituent attached to N-3 of 1,3-thiazinan-4-one ring increased both selectivity and



Scheme 1. Reagents and conditions: (a) toluene, reflux, 72 h; (b) H_2O_2 30%, WO_3, 25 °C, 6 h; (c) DMF, 25 °C, 24 h; (d) H_2O_2 30%, WO_3, 25 °C, 4 h; (e) toluene, reflux, 24 h.

Table 1
In vitro COX-1 and COX-2 enzyme inhibition data



Compound	R	IC_{50}[a] (μM)		COX-2 S.I.[b]
		COX-1	COX-2	
11a	Benzyl	17.15	0.06	285.8
11b	Phenethyl	15.98	0.07	228.3
11c	Cyclohexyl	ND	ND	ND[c]
11d	Propyl	14.12	0.11	128.4
11e	Butyl	14.8	0.08	185
11f	Pentyl	14.91	0.08	186.4
Celecoxib		24.3	0.06	405

[a] Values are mean values of two determinations acquired using an ovine COX-1/COX-2 assay kit, where the deviation from the mean is <10% of the mean value.
[b] In vitro COX-2 selectivity index (COX-1 IC_{50}/COX-2 IC_{50}).
[c] Not determined.

potency for COX-2 inhibitory activity. However, compound **11b** showed less selectivity and potency for COX-2 isozyme compared with compound **11a** that may be explained by steric parameter. According to these results, 3-benzyl-2-(4-methyl sulfonyl phenyl)-1,3-thiazinan-4-one **11a** was the most potent (IC_{50} = 0.06 μM), and selective (S.I. = 285.8), COX-2 inhibitor among the synthesized compounds. It was as potent as celecoxib (IC_{50} = 0.06 μM; S.I. = 405) in terms of COX-2 inhibitory activity but showed less selectivity. These data suggest that the compound **11a** should inhibit the biosynthesis of prostaglandins via the cyclooxgenase pathway at sites of inflammation and be devoid of ulcerogenicity due to the absence of COX-1 inhibition.

The orientation of the highly potent and selective COX-2 inhibitor, 3-benzyl-2-(4-methylsulfonylphenyl)-1,3-thiazinan-4-one **11a** in the COX-2 active site was examined by a docking experiment (Fig. 1).[22,23] This molecular modeling shows that it binds in the primary binding site such that the C-2 *para*-SO_2Me substituent inserts into the secondary pocket present in COX-2 isozyme. One of the *O*-atoms of *p*-SO_2Me forms a hydrogen bonding interaction with amino group of Arg^{513} (distance = 4.0 Å) whereas the other *O*-atom is close to other hydrogen of this amino acid (distance = 5.4 Å). The C=*O* of the central thiazinan-4-one is almost close to (distance = 5.9 Å) O*H* of Ser^{530}. In addition, the phenyl ring of benzyl substituent is very close to phenyl ring of Tyr^{348} which may involve with hydrophobic interaction. These observations together with experimental results provide a good explanation for the potent and selective inhibitory activity of **11a**.

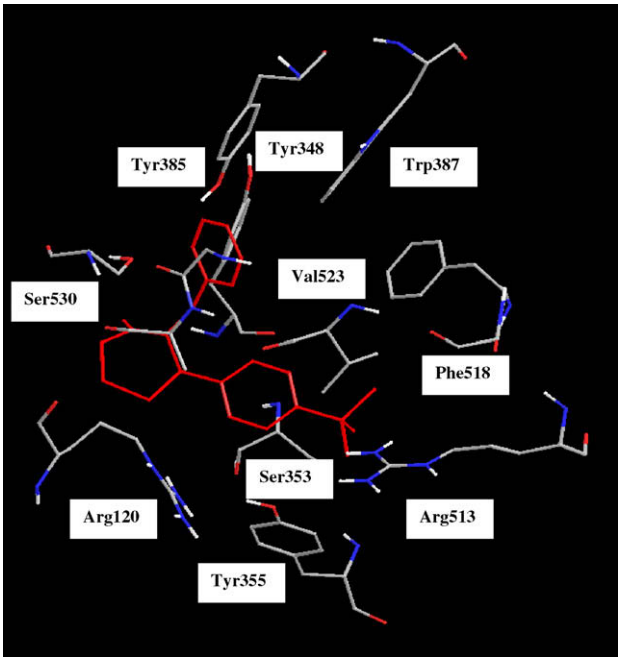


Figure 1. Compound **5b** 3-benzyl-2-(4-methylsulfonylphenyl)-1,3-thiazinane-4-one docked in the active site of murine COX-2 isozyme.

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References and notes

1. Smith, W. L.; DeWitt, D. L.; Garavito, R. M.; Raz, A. *Ann. Rev. Biochem.* **2000**, *69*, 145.
2. Vane, J. R.; Bakhle, Y. S.; Botting, R. M. *Ann. Rev. Pharmacol. Toxicol.* **1998**, *38*, 97.04.
3. Xie, W. L.; Chipman, J. G.; Robertson, D. L.; Erikson, R. L.; Simmons, D. L. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 2692.
4. Smith, W. L.; DeWitt, D. L. *Adv. Immunol.* **1996**, *62*, 167.
5. Herschman, H. R. *Biochem. Biophys. Acta* **1996**, *1299*, 125.
6. Kawamori, T.; Rao, C. V.; Seibert, K.; Reddy, B. S. *Cancer Res.* **1998**, *58*, 409.
7. Kanaoka, S.; Takai, T.; Yoshida, K. *Adv. Clin. Chem.* **2007**, *43*, 59.
8. Allison, C. E.; Howatson, A. G.; Torrance, C. J.; Lee, F. D.; Russel, R. L. *N. Eng. J. Med.* **1992**, *327*, 749.
9. Eberhart, C. E.; DuBois, R. N. *Gasteroenterology* **1995**, *109*, 285.
10. Vane, J. R.; Botting, R. M. *Inflamm. Res.* **1998**, *47*, S78.
11. Penning, T. D.; Tally, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347.
12. Riendeau, D.; Percival, M. D.; Brideau, C.; Dube, C. S.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Gordon, R.; Greig, G.; Guay, J.; Girard, Y.; Prasit, P.; Zamboni, R.; Rodger, I. W.; Gresser, M.; Ford-Hutchinson, A. W.; Young, R. N.; Chan, C. C. *J. Pharmacol. Exp. Ther.* **2002**, *296*, 558.
13. Prasit, P.; Wang, Z.; Brideau, C.; Chan, C.-C.; Charlson, S.; Cromlish, W.; Ethier, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Gauthier, J. Y.; Gordon, R.; Guay, J.; Gresser, M.; Kargman, S.; Kennedy, B.; Leblanc, Y.; Leger, S.; Mancini, J.; O_Neil, G. P.; Quellet, M.; Percival, M. D.; Perrier, H.; Riendeau, D.; Rodger, I.; Tagari, P.; Therien, M.; Vikers, P.; Wong, E.; Xu, L.-J.; Young, R. N.; Zamboni, R.; Boyce, S.; Rupniak, N.; Forrest, M.; Visco, D.; Patrick, D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1773.
14. Friesen, R. W.; Dube, D.; Fortin, R.; Frenette, R.; Prescott, S.; Cromlish, W.; Greig, G. M.; Kargman, S.; Wong, E.; Chan, C. C.; Gordon, R.; Xu, L. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2677.
15. Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775.
16. Zarghi, A.; Rao, P. N. P.; Knaus, E. E. *Bioorg. Med. Chem.* **2007**, *15*, 1056.
17. Zarghi, A.; Najafnia, L.; Daraee, B.; Dadrass, O. G.; Hedayati, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5634.
18. Dogné, J. M.; Supuran, C. T.; Pratico, D. *J. Med. Chem.* **2005**, *48*, 2251.
19. Mason, R. P.; Walter, M. F.; McNulty, H. P.; Lockwood, S. F.; Byun, J.; Day, C. A.; Jacob, R. F. *J. Cardivasc. Pharmacol.* **2006**, *47*, S7.
20. Surrey, A. R.; Webb, W. G.; Gesler, R. M. *J. Am. Chem. Soc.* **1957**, *80*, 3469.
21. COX-1 and COX-2 assays: The assay was performed using an enzyme chemiluminescent kit (catalog number 760101, Cayman chemical, MI, USA). The Cayman chemical chemiluminescent COX (ovine) inhibitor screening assay utilizes the heme-catalyzed hydroperoxidase activity of ovine cyclooxygenases to generate luminescence in the presence of a cyclic naphthalene hydrazide and the substrate arachidonic acid. Arachidonate-induced luminescence was shown to be an index of real-time catalytic activity and demonstrated the turnover inactivation of the enzyme. Inhibition of COX activity, measured by luminescence, by a variety of selective and nonselective inhibitors showed potencies similar to those observed with other in vitro and whole cell methods.[7]
22. Docking studies were performed using Autodock software Version 3.0. The coordinates of the X-ray crystal structure of the selective COX-2 inhibitor SC-558 bound to the murine COX-2 enzyme was obtained from the RCSB Protein Data Bank (1cx2) and hydrogens were added. The ligand molecules were constructed using the Builder module and were energy minimized for 1000 iterations reaching a convergence of 0.01 kcal/mol Å. The energy minimized

ligands were superimposed on SC-558 in the PDB file 1cx2 after which SC-558 was deleted. The purpose of docking is to search for favourable binding configuration between the small flexible ligands and the rigid protein. Protein residues with atoms greater than 7.5 Å from the docking box were removed for efficiency. Searching is conducted within a specified 3D docking box using annealing based on the Monte Carlo method and MMFF94 molecular mechanics force field for 8000 iterations. These docked structures were very similar to the minimized structures obtained initially. The quality of the docked structures was evaluated by measuring the intermolecular energy of the ligand–enzyme assembly.

23. Kurumbail, R. G.; Stevens, A. M.; Gierse, J. K.; McDonald, J. J.; Stegeman, R. A.; Pak, J. Y.; Gildehaus, D.; Miyashiro, J. M.; Penning, T. D.; Seibert, K.; Isakson, P. C.; Stallings, W. C. *Nature* **1996**, *384*, 644.
24. *Analytical data for* **10a**. Yield, 11%; yellow oil; IR (neat): ν cm^{-1} 1650 (C=O) cm^{-1}; MS: *m/z* (%) 329.3 (M^+, 35), 241.1 (45), 224.2 (60), 192.1 (70), 178.1 (40), 137.0 (70), 91.0 (100), 77.2 (40); ^1H NMR ($CDCl_3$): δ ppm 2.55 (S, 3H, SCH_3), 2.71–3.01 (m, 4H, CH_2–CH_2), 3.60 (d, 1H, CH_2N, J = 15.2 Hz), 4.40 (d, 1H, CH_2N, J = 15.2 Hz), 5.41 (S, 1H, CH), 7.18 (d, 2H, 4-methylthiophenyl H_3 and H_5, J = 8.3 Hz), 7.24–7.43 (m, 5H, phenyl), 7.36 (d, 2H, 4-methylthiophenyl H_2 and H_6, J = 8.3 Hz). Anal. Calcd for $C_{18}H_{19}NOS_2$: C, 65.62; H, 5.81; N, 4.25. Found: C, 65.32; H, 5.60; N, 4.08. *Compound* **10b**. Yield, 12%; yellow oil; IR (neat): ν cm^{-1} 1650 (C=O); MS: *m/z* (%) 343.1 (M^+, 40), 254.2 (50), 238.9 (90), 163.8 (100), 137.0 (85), 116.9 (85), 105.1 (60), 77.1 (65); ^1H NMR ($CDCl_3$): δ ppm 2.41 (s, 3H, SMe), 2.52–2.86 (m, 6H, $COCH_2CH_2$ and Phenyl CH_2), 2.90 (m, 1H, CH_2N), 4.26 (m, 1H, CH_2N), 5.06 (s, 1H, CH), 7.02 (d, 2H, 4-methylthiophenyl H_3 and H_5, J = 8.1 Hz), 7.10–7.17 (m, 5H, phenyl), 7.22 (d, 2H, 4-methylthiophenyl H_2 and H_6, J = 8.1 Hz). Anal. Calcd for $C_{19}H_{21}NOS_2$: C, 66.43; H, 6.16; N, 4.08. Found: C, 66.79; H, 6.40; N, 4.21. *Compound* **10c**. Yield, 10%; yellow oil; IR (neat): ν cm^{-1} 1650 (C=O); MS: *m/z* (%) 321.2 (M^+, 30), 233.2 (100), 218.2 (30), 190.1 (40), 178.1 (45), 150.0 (90), 137.0 (100), 109.1 (30), 83.1 (30). Anal. Calcd for $C_{17}H_{23}NOS_2$: C, 63.51; H, 7.21; N, 4.36. Found: C, 63.22; H, 7.60; N, 4.18. *Compound* **11a**. Yield, 35%; yellow crystalline powder, mp 193–194 °C; IR (KBr): ν cm^{-1} 1670 (C=O), 1320, 1170 (SO_2); MS: *m/z* (%) 361.3 (M^+, 10), 289.4 (10), 251.1 (20), 212.3 (10), 165.9 (100), 140.4 (20), 109.1 (100), 83.1 (100); ^1H NMR(DMSO-d_6) δ ppm 3.27 (s, 3H, SO_2Me), 3.05–3.39 (m, 4H, CH_2–CH_2), 3.91 (d, 1H, CH_2N, J = 15.4 Hz), 4.97 (d, 1H, CH_2N, J = 15.4 Hz), 6.13 (s, 1H, CH), 7.20–7.27 (m, 5H, phenyl), 7.71 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.4 Hz), 7.96 (d, 4-methylsulfonylphenyl H_3 and H_5, J = 8.4 Hz). Anal. Calcd for $C_{18}H_{19}NO_3S_2$: C, 59.81; H, 5.30; N, 3.87. Found: C, 59.62; H, 5.41; N, 4.02. *Compound* **11b**. Yield, 40%; yellow semisolid; IR (KBr): ν cm^{-1} 1670 (C=O), 1330, 1150 (SO_2); MS: *m/z* (%) 375.1 (M^+, 5), 286.2 (15), 196.1 (45), 117.2 (95), 90.0 (100), 77.1 (30); ^1H NMR ($CDCl_3$): δ ppm 2.68–2.87 (m, 4H, $COCH_2CH_2$), 3.05 (s, 1H, SO_2Me), 3.07–3.10 (m, 2H, CH_2 Phenyl), 3.17 (m, 1H, CH_2N), 4.23 (m, 1H, CH_2N), 5.01 (s, 1H, CH), 7.09 (d, Phenyl H_2 and H_6, J = 7.1 Hz), 7.15–7.24 (m, 3H, Phenyl H_3–H_5), 7.48 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.4 Hz) 7.96 (d, 2H, 4-methylsulfonylphenyl H_3 and H_5, J = 8.4 Hz). Anal. Calcd for $C_{19}H_{21}NO_3S_2$: C, 60.77; H, 5.64; N, 3.73. Found: C, 60.52; H, 5.50; N, 3.88. *Compound* **11c**.Yield, 75%, yellow powder, mp 138–140 °C; IR (KBr): ν cm^{-1} 1660 (C=O), 1300, 1150 (SO_2); MS: *m/z* (%) 353.1 (M^+, 5), 265.0 (48), 202.0 (25), 155.0 (100), 139.1 (35), 73.1 (34); ^1H NMR($CDCl_3$): δ ppm 1.14–1.88 (m, 10H, cyclohexyl), 2.52 (m, 2H, CH_2S), 2.90 (s, 1H, SO_2Me), 2.96 (m, 2H, CH_2CO), 3.76 (m, 1H, CHN), 7.72 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.3 Hz), 8.08 (d, 2H, 4-methylsulfonyl phenyl H_3 and H_5, J = 8.3 Hz). Anal. Calcd for $C_{17}H_{23}NO_3S_2$: C, 57.76; H, 6.56; N, 3.96. Found: C, 57.42; H, 6.80; N, 4.02. *Compound* **11d**. Yield, 12%, yellow crystalline powder, mp 152–153 °C; IR (KBr): ν cm^{-1} 1670 (C=O), 1300, 1150 (SO_2); MS: *m/z* (%) 313.2 (M^+, 55), 233.1 (25), 206.1 (30), 179.1 (15), 91.0 (100), 77.0 (40); ^1H NMR($CDCl_3$): δ ppm 0.99 (t, 3H, CH_3), 1.68 (m, 2H, CH_2), 2.55–2.90 (m, 4H, $COCH_2CH_2$), 3.05 (s, 3H, SO_2Me), 3.94 (t, 2H, CH_2N), 5.53 (s, 1H, CH), 7.93 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.5 Hz), 8.40 (d, 2H, 4-methylsulfonylphenyl H_3 and H_5, J = 8.5 Hz). Anal. Calcd for $C_{14}H_{19}NO_3S_2$: C, 53.65; H, 6.11; N, 4.47. Found: C, 53.42; H, 5.90; N, 4.38. *Compound* **11e**. Yield, 45%, yellow crystalline powder, mp 159–160 °C; IR (KBr): ν cm^{-1} 1670 (C=O), 1310, 1150 (SO_2); MS: *m/z* (%) 327.2 (M^+, 15), 240.2 (40), 196.1 (40), 159.1 (15), 117.1 (100), 91.0 (60), 77.0 (50); ^1H NMR($CDCl_3$): δ ppm 0.96 (t, 3H, CH_3), 1.35 (m, 2H, CH_2), 1.63 (m, 2H, CH_2), 2.74–2.89 (m, 4H, $COCH_2CH_2$), 3.12 (s, 3H, SO_2Me), 4.20 (t, 2H, CH_2N), 5.59 (s, 1H, CH), 7.49 (d, 2H, 4-methyl sulfonylphenyl H_2 and H_6, J = 8.3 Hz), 8.01 (d, 2H, 4-methylsulfonylphenyl H_3 and H_5, J = 8.3 Hz). Anal. Calcd for $C_{15}H_{21}NO_3S_2$: C, 55.02; H, 6.46; N, 4.28. Found: C, 55.32; H, 6.65; N, 4.40. *Compound* **11f**. Yield, 44%, yellow crystalline powder, mp 167–168 °C; IR (KBr): ν cm^{-1} 1670 (C=O), 1310, 1160 (SO_2); MS: *m/z* (%) 341.1 (M^+, 30), 254.2 (60), 238.1 (65), 196.1 (50), 131.1 (25), 117.1 (100), 91.0 (50), 77.0 (30); ^1H NMR ($CDCl_3$): δ ppm 0.93 (t, 3H, CH_3), 1.30 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 2.73–2.87 (m, 4H, $COCH_2CH_2$), 2.76 (m, 2H, CH_2), 3.11 (s, 3H, SO_2Me), 4.21 (t, 2H, CH_2N), 5.59 (s, 1H, CH), 7.50 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.3 Hz), 8.00 (d, 2H, 4-methylsulfonyl phenyl H_3 and H_5, J = 8.3 Hz). Anal. Calcd for $C_{16}H_{23}NO_3S_2$: C, 56.27; H, 6.79; N, 4.10. Found: C, 56.52; H, 6.99; N, 4.12.
25. *Analytical data for* **12a**. Yield, 20%, yellow oil; IR (neat): ν cm^{-1} 1650 (C=N); MS: *m/z* (%) 193.1 (M^+, 30), 178.1 (15), 136.1 (50), 120.0 (100), 91.1 (30), 77.1 (20). *Compound* **12b**. Yield, 22%, yellow oil; IR (neat): ν cm^{-1} 1650 (C=N); MS: *m/z* (%) 207.3 (M^+, 25), 192.2 (45), 178.2 (35), 164.0 (45), 150.1 (40), 136.9 (55), 117.2 (100), 91.1 (30). *Compound* **12c**. Yield, 16%, pale yellow powder; IR (KBr): ν cm^{-1} 1650 (C=N); MS: *m/z* (%) 253.2 (M^+, 15), 238.1 (90), 224.1 (20), 210.1 (60), 196.0 (50), 182.0 (50), 132.1 (30), 117.0 (100), 91.1 (20), 77.1 (25). *Compound* **13a**. Yield, 18%, pale yellow powder; IR (KBr): ν cm^{-1} 1300, 1150 (SO_2); MS *m/z* (%): 225.0 (M^+, 20), 196.0 (85), 146.1 (40), 117.0 (100), 91.0 (50), 77.0 (25); ^1H NMR ($CDCl_3$): δ ppm 0.99 (t, 3H, CH_3), 1.63 (m, 2H, CH_2), 3.05 (s, 3H, SO_2Me), 3.42 (t, 2H, CH_2N), 7.92 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.4 Hz) 7.99 (d, 2H, 4-methylsulfonyl phenyl H_3 and H_5, J = 8.4 Hz); Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.34; H, 6.91; N, 6.30. *Compound* **13b**. Yield, 17%, pale yellow powder; IR (KBr): ν cm^{-1} 1310, 1150 (SO_2); MS *m/z* (%): 239.1 (M^+, 10), 210. 0 (15), 196.0 (35), 137.1 (25), 117.0 (100), 91.0 (60), 77.0 (70). Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found: C, 60.39; H, 7.44; N, 5.98. *Compound* **13c**. Yield, 15%, pale yellow powder; IR (KBr): ν cm^{-1} 1310, 1150 (SO_2); MS *m/z* (%): 253.1 (M^+, 10), 238.1 (85), 210.1 (60), 196.0 (50), 182.0 (50), 132.1 (30), 117.0 (100), 90.1 (75), 77.1 (25); Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53. Found: C, 61.88; H, 7.77; N, 5.60. Satisfactory analysis for C, H, N was obtained for all the compounds within ±0.4% of the theoretical values.